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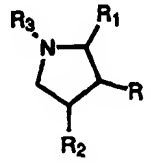

(I)

(57) Abstract

A compound of formula (I), or a pharmaceutically acceptable salt thereof is disclosed, as well as processes for and intermediates in the preparation thereof, and a method of antagonizing endothelin.

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PYRROLIDINE CARBOXYLIC ACID DERIVATIVES AS ENDOTHELIN ANTAGONISTS

This is a continuation-in-part application of US Serial No. 08/877,187 filed June 17, 1997.

Technical Field

The present invention relates to compounds which are endothelin antagonists, processes for making such compounds, synthetic intermediates employed in these processes and methods and compositions for antagonizing endothelin.

Background of the Invention

Endothelin (ET) is a 21 amino acid peptide that is produced by endothelial cells. ET is produced by enzymatic cleavage of a Trp-Val bond in the precursor peptide big endothelin (Big ET). This cleavage is caused by an endothelin converting enzyme (ECE). Endothelin has been shown to constrict arteries and veins, increase mean arterial blood pressure, decrease cardiac output, increase cardiac contractility in vitro, stimulate mitogenesis in vascular smooth muscle cells in vitro, contract non-vascular smooth muscle including guinea pig trachea, human urinary bladder strips and rat uterus in vitro, increase airway resistance in vivo, induce formation of gastric ulcers, stimulate release of atrial natriuretic factor in vitro and in vivo, increase plasma levels of vasopressin, aldosterone and catecholamines, inhibit release of renin in vitro and stimulate release of gonadotropins in vitro.

It has been shown that vasoconstriction is caused by binding of endothelin to its receptors on vascular smooth muscle (Nature 332 411 (1988), FEBS Letters 231 440 (1988) and Biochem. Biophys. Res. Commun. 154 868 (1988)). An agent which suppresses endothelin production or an agent which binds to endothelin or which inhibits the binding of endothelin to an endothelin receptor will produce beneficial effects in a variety of therapeutic areas. In fact, an anti-endothelin antibody has been shown, upon intrarenal infusion, to ameliorate the adverse effects of renal ischemia on renal vascular resistance and glomerular filtration rate (Kon, et al., J. Clin. Invest. 83 1762 (1989)). In addition, an anti-endothelin antibody attenuated the nephrotoxic effects of intravenously administered cyclosporin (Kon, et al., Kidney Int. 37 1487 (1990)) and attenuated infarct size in a coronary artery

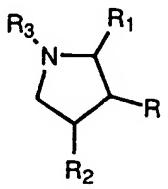
Clozel et al. (Nature 365: 759-761 (1993)) report that Ro 46-2005, a nonpeptide ET-A/B antagonist, prevents post-ischaemic renal vasoconstriction in rats, prevents the decrease in cerebral blood flow due to subarachnoid hemorrhage (SAH) in rats, and decreases MAP in sodium-depleted squirrel monkeys when dosed orally. A similar effect of a linear tripeptide-like ET-A antagonist, BQ-485, on arterial caliber after SAH has also been recently reported (S.Itoh, T. Sasaki, K. Ide, K. Ishikawa, M. Nishikibe, and M. Yano, Biochem. Biophys. Res. Comm. , 195: 969-75 (1993). These results indicate that agents which antagonize ET/ET receptor binding will provide therapeutic benefit in the indicated disease states.

Two structurally related endothelin receptors have been cloned, sequenced and characterized (Hosada, K.; Nakao, K.; Arai, H.; Suga, S.; Ogawa, Y.; Mukoyama, M.; Shirakami, G.; Saito, Y.; Nakanishi, S.; Imura, H. FEBS Lett. 1991, 187, 23-26: Sakamoto, A.; Yanagisawa, M.; Sakurai, T.; Takuwa, Y.; Yanagisawa, H.; Masaki, T. Biochem. Biophys. Res. Commun. 1991, 178, 656-663). Each binds the three endothelin isopeptides with differing affinities; the ET_A receptor displays affinity for ET-1 and ET-2 over ET-3, while the ET_B receptor is non-isopeptide selective. Originally described as a vasodilatory receptor due to its mediation of nitric oxide release (DeNucci,G.; Thomas, R.; D'Orleans-Juste, P.; Antunes, E.; Walder, C.; Warner, T. D.; Vane, J. R. Proc. Natl. Acad. Sci. U.S.A. 1988, 85, 9797-9800), it is now apparent that the ET_B receptor is responsible for a greater diversity of physiologic function. Current research suggests a role for ET_B mediated responses in certain disease states including established pulmonary hypertension (McCulloch, K. M.; MacLean, M. R.; J. Cardiovasc. Pharmacol. 1995, 26(Suppl. 3), S169-S176), contractile dysfunction associated with benign prostatic hyperplasia (Webb, M. L.; Chao, C.-C.; Rizzo, M.; Shapiro, R. A.; Neubauer, M.; Liu, E. C. K.; Aversa, C. R.; Brittain, R. J.; Treiger, B. Mol. Pharmacol. 1995, 47, 730-737; Webb, M. L.; Meek, T. D. Med. Res. Rev. 1997, 17, 17-67), myocardial infarction (Vitola, J. V.; Forman, M. B.; Holsinger, J. P.; Kawana, M.; Atkinson, J. B.; Quertermous, T.; Jackson, E. K.; Murray, J.J. J. Cardiovasc. Pharmacol. 1996, 28, 774-783), and atherosclerosis (Dagassan, P. H.; Breu, V.; Clozel, M.; Kunzli, A.; Vogt, P, Turina, M.; Kiowski, Clozel, J. -P. J. Cardiovasc. Pharmacol. 1996, 27, 147-153). Our group has previously reported the discovery of a series of pyrrolidine-3-carboxylic acids which which bind potently and selectively to the ET_A receptor subtype (Winn, M.; von Geldern, T. W.; Opgenorth, T. J.; Jae, H. -S.; Tasker, A. S.; Boyd, S. A.; Kester, J. A.; Mantei, R. A.; Bal, R. B.; Sorensen, B. K.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D. B.; Novosad, E. I.;

Hernandez, L.; Marsh, K. C. J. Med. Chem. 1996, 39, 1039-1048). The compounds claimed in the current invention differ from those previously described and are unique in that they bind potently and selectively to the ET_B subtype, blocking the actions of the endothelins on these receptors. As such, they may find utility in the treatment of diseases that are mediated by the ET_B receptor.

Disclosure of the Invention

In accordance with the present invention there are compounds of the formula (I):



(I)

wherein

R is $-(CH_2)_m-W$ wherein m is an integer from 0 to 6 and W is

(a) $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

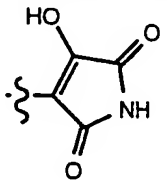
(i) hydroxy,

(j) alkoxy,

(k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,

(m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,



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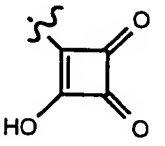
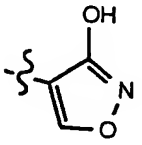
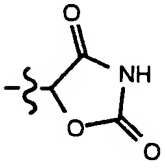
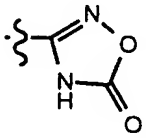
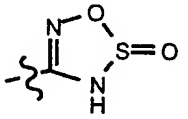
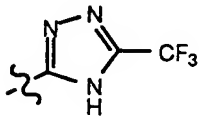
(o)  ,

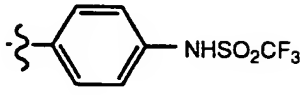
(p)  ,

(q)  ,

(r)  ,

(s)  ,

(t)  , or

(u)  ;

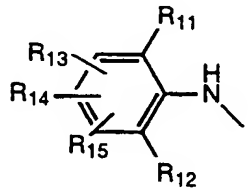
R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N\text{-}R_{cc}$- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

R_3 is $R_4\text{-}C(O)\text{-}R_5$- or $R_6\text{-}S(O)_2\text{-}R_7$- wherein R_5 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) $\text{-}N(R_{20})\text{-}R_8$- or $\text{-}R_{8a}\text{-}N(R_{20})\text{-}R_8$- wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene and alkenylene; and

R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl or cycloalkylalkyl or (v) -O-R_9- or -R_{9a}-O-R_9- wherein R_9 and R_{9a} are independently selected from alkylene;

R_7 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) -N(R_{21})-R_{10}- or -R_{10a}-N(R_{21})-R_{10}- wherein R_{10} and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and R_{21} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

wherein R_4 and R_6 are



(i)

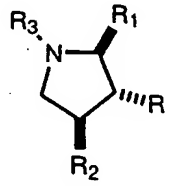
wherein R_{11} and R_{12} are independently selected from the

group consisting of loweralkyl, cyano, alkoxy, halo, haloalkyl and phenyl and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano; or

(ii) heterocyclic(amino),

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the invention is a compound of formula (II)



(II)

wherein the substituents -R_2, -R and -R_1 exist in a *trans,trans* relationship and R, R_1, R_2, and R_3 are as defined above.

A more preferred embodiment of the invention is a compound of formula (I) or (II) wherein R_3 is R_4-C(O)-R_5- wherein R_4 is as defined above and R_5 is alkylene or R_3 is R_6-S(O)$_2$-R_7- wherein R_7 is alkylene and R_6 is defined as above.

An even more preferred embodiment of the invention is a compound of formula (I) or (II) wherein R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group or R is tetrazolyl or R is -C(O)-NHS(O)$_2$$R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, R_1 and R_2 are independently selected from

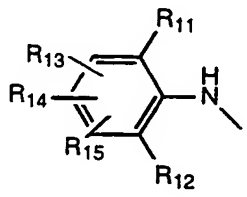
(i) loweralkyl, (ii) cycloalkyl, (iii) substituted and unsubstituted aryl, and (iv) substituted or unsubstituted heterocyclic, and R_3 is R_4-C(O)-R_5- wherein R_4 is as defined above and R_5 is alkylene or R_3 is R_6-$S(O)_2$-R_7- wherein R_7 is alkylene and R_6 is defined as above.

A yet more preferred embodiment of the invention is a compound of formula (I) or (II) wherein R is -$C(O)_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-$NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, R_1 is (i) alkoxyalkyl, (ii) cycloalkyl, (iii) phenyl, (iv) pyridyl, (v) furanyl or (vi) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is R_4-C(O)-R_5- wherein R_4 is as defined above and R_5 is alkylene or R_3 is R_6-$S(O)_2$-R_7- wherein R_7 is alkylene and R_6 is defined as above.

Another yet more preferred embodiment of the invention is a compound of formula (I) or (II) wherein R is -$C(O)_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-$NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, R_1 is (i) alkoxyalkyl, (ii) cycloalkyl, (iii) phenyl, (iv) pyridyl, (v) furanyl or (vi) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is R_4-C(O)-R_5- wherein R_4 is as defined above and R_5 is alkylene.

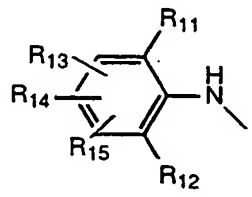
A still more preferred embodiment of the invention is a compound of formula (I) or (II) wherein R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_4 is as defined above and R_5 is alkylene.

A most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_4 is



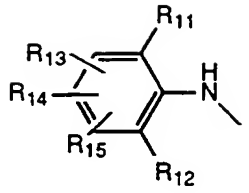
wherein R_{11} and R_{12} are independently selected from loweralkyl, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is alkylene.

A most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_4 is



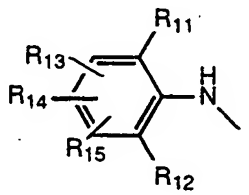
wherein R_{11} and R_{12} are independently selected from the group consisting of lower alkyl, alkoxy and halo, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_4 is



wherein R_{11} and R_{12} are independently selected from the group consisting of methyl, ethyl, and isopropyl, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_4 is



wherein R_{11} and R_{12} are independently selected from the group consisting of methyl, ethyl, and isopropyl, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is methylene.

The present invention also relates to processes for preparing the compounds of formula (I) and (II) and to the synthetic intermediates employed in these processes.

The present invention also relates to a method of antagonizing endothelin in a mammal (preferably a human) in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of formula (I) or (II).

The invention further relates to endothelin antagonizing compositions comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of formula (I) or (II).

The compounds of the invention comprise two or more asymmetrically substituted carbon atoms. As a result, racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13 - 30.

The term "carboxy protecting group" as used herein refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* , for example by enzymatic hydrolysis, to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C_1 to C_8 alkyl (e.g., methyl, ethyl or tertiary butyl and the like); haloalkyl; alkenyl; cycloalkyl and substituted derivatives thereof such as cyclohexyl, cyclopentyl and the like; cycloalkylalkyl and substituted derivatives thereof such as cyclohexylmethyl, cyclopentylmethyl and the like; arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-

indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxyl)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undersirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-

dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to an alkyl group as defined herein appended to the parent molecular moiety through a carbonyl (-C(O)-) group. Examples of alkanoyl include acetyl, propionyl and the like.

The term "alkanoylamino" as used herein refers to an alkanoyl group as previously defined appended to an amino group. Examples alkanoylamino include acetamido, propionamido and the like.

The term "alkanoylaminoalkyl" as used herein refers to R_{43}-NH-R_{44}- wherein R_{43} is an alkanoyl group and R_{44} is an alkylene group.

The term "alkanoyloxyalkyl" as used herein refers to R_{30}-O-R_{31}- wherein R_{30} is an alkanoyl group and R_{31} is an alkylene group. Examples of alkanoyloxyalkyl include acetoxymethyl, acetoxyethyl and the like.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon radical containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon double bond. Alkenyl groups include, for example, vinyl (ethenyl), allyl (propenyl), butenyl, 1-methyl-2-buten-1-yl and the like.

The term "alkenylene" denotes a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include -CH=CH-, -CH_2CH=CH-, -C(CH_3)=CH-, -CH_2CH=CHCH_2-, and the like.

The term "alkenyloxy" as used herein refers to an alkenyl group, as previously defined, connected to the parent molecular moiety through an oxygen (-O-) linkage. Examples of alkenyloxy include allyloxy, butenyloxy and the like.

The term "alkoxy" as used herein refers to R_{42}O- wherein R_{42} is a loweralkyl group, as defined herein. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, iso-butoxy, tert-butoxy, and the like.

The term "alkoxyalkoxy" as used herein refers to $R_{80}O$-$R_{81}O$- wherein R_{80} is loweralkyl as defined above and R_{81} is alkylene. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like.

The term "alkoxyalkoxyalkoxy" as used herein refers to $R_{82}O$-$R_{83}O$-$R_{84}O$- wherein R_{82} is loweralkyl as defined above and R_{83} and R_{84} are alkylene. Representative examples of alkoxyalkoxyalkoxy groups include methoxyethoxymethoxy, ethoxymethoxymethoxy, t-butoxymethoxymethoxy and the like.

The term "(alkoxyalkyl)sulfonyl" as used herein refers to R_{85}-O-R_{86}-$S(O)_2$-, wherein R_{85} is loweralkyl and R_{86} is alkylene.

The term "alkoxyalkoxyalkyl" as used herein refers to an alkoxyalkoxy group as previously defined appended to an alkyl radical. Representative examples of alkoxyalkoxyalkyl groups include methoxyethoxyethyl, methoxymethoxymethyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl radical as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like.

The term "alkoxycarbonyl" as used herein refers to an alkoxyl group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like.

The term "alkoxycarbonylalkenyl" as used herein refers to an alkoxycarbonyl group as previously defined appended to an alkenyl radical. Examples of alkoxycarbonylalkenyl include methoxycarbonylethenyl, ethoxycarbonylethenyl and the like.

The term "alkoxycarbonylalkyl" as used herein refers to R_{34}-C(O)-R_{35}- wherein R_{34} is an alkoxy group and R_{35} is an alkylene group. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylmethyl and the like.

The term "alkoxycarbonylaminoalkyl" as used herein refers to R_{38}-C(O)-NH-R_{39}- wherein R_{38} is an alkoxy group and R_{39} is an alkylene group. Examples of alkoxycarbonylaminoalkyl include methoxycarbonylaminoethyl and the like.

The term "alkoxycarbonyloxyalkyl" as used herein refers to R_{36}-C(O)-O-R_{37}- wherein R_{36} is an alkoxy group and R_{37} is an alkylene group. Examples of alkoxycarbonyloxyalkyl include (ethoxycarbonyloxy)methyl and the like.

The term "(alkoxycarbonyl)thioalkoxy" as used herein refers to an alkoxycarbonyl group as previously defined appended to a thioalkoxy radical. Examples of (alkoxycarbonyl)thioalkoxy include methoxycarbonylthiomethoxy, ethoxycarbonylthiomethoxy and the like.

The terms "alkyl" and "loweralkyl" as used herein refer to straight or branched chain alkyl radicals containing from 1 to 15 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkylamino" as used herein refers to R_{51}NH- wherein R_{51} is a loweralkyl group, for example, ethylamino, butylamino, and the like.

The term "(alkylamino)alkoxy" as used herein refers R_{52}NH-R_{53}-O- wherein R_{52} is loweralkyl and R_{53} is alkylene.

The term "alkylaminocarbonyl" as used herein refers to an alkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of alkylaminocarbonyl include methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl and the like.

The term "alkylaminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended an alkylaminocarbonyl group.

The term "alkylaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylaminocarbonyl group.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to R_{40}-C(O)-NH-R_{41}- wherein R_{40} is an alkylamino group and R_{41} is an alkylene group.

The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 15 carbon atoms by the removal of two hydrogen atoms, for example -CH_2-, -CH_2CH_2-, -$CH(CH_3)$-, -$CH_2CH_2CH_2$-, -$CH_2C(CH_3)_2CH_2$- and the like.

The term "alkylsulfonyl" refers to an alkyl group appended to the parent molecular moiety through a sulfonyl group -$S(O)_2$-. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, isopropylsulfonyl and the like.

The term "(alkylsulfonyl)amino" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a sulfonylamino

(-$S(O)_2$-NH-) group. Examples of (alkylsulfonyl)amino include methylsulfonylamino, ethylsulfonylamino, isopropylsulfonylamino and the like.

The term "(alkylsulfonyl)alkoxy" as used herein refers to an alkylsulfonyl group as previously defined appended to the parent molecular moiety through a alkoxy group. Examples of (alkylsulfonyl)alkoxy include methylsulfonylmethoxy, ethylsulfonylethoxy, isopropylsulfonylisopropoxy and the like.

The term "(alkylthio)alkoxy" as used herein refers to R_{54}-S-R_{55}-O-, wherein R_{54} is loweralkyl and R_{55} is alkylene.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon radical containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include -C≡C-H, H-C≡C-CH_2-, H-C≡C-$CH(CH_3)$-, CH_3-C≡ C-CH_2-, and the like.

The term "aminocarbonyl" as used herein refers to H_2N-C(O)- .

The term "aminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended an aminocarbonyl ($NH_2C(O)$-) group.

The term "aminocarbonylalkoxy" as used herein refers to H_2N-C(O)- appended to an alkoxy group as previously defined. Examples of aminocarbonylalkoxy include aminocarbonylmethoxy, aminocarbonylethoxy and the like.

The term "aminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an aminocarbonyl ($NH_2C(O)$-) group.

The term "aroyloxyalkyl" as used herein refers to R_{32}-C(O)-O-R_{33}- wherein R_{32} is an aryl group and R_{33} is an alkylene group. Examples of aroyloxyalkyl include benzoyloxymethyl, benzoyloxyethyl and the like.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkenyloxy, alkoxy, alkoxyalkoxy, alkoxycarbonyl, alkoxyalkoxyalkoxy, (cycloalkyl)alkoxy, cycloalkoxy, (alkylamino)alkoxy, (alkylthio)alkoxy, alkoxycarbonylalkenyl, (alkoxycarbonyl)thioalkoxy, thioalkoxy, amino, alkylamino, dialkylamino, (dialkylamino)alkyl, (dialkylamino)alkoxy, aminocarbonyl, aminocarbonylalkoxy, alkanoylamino, arylalkoxy, aryloxy, mercapto, cyano, nitro, carboxaldehyde, carboxy, carboxyalkenyl, carboxyalkoxy, carboxamide, alkylsulfonyl, (alkylsulfonyl)amino, (alkylsulfonyl)alkoxy, (alkoxyalkyl)sulfonyl, cyanoalkoxy, (heterocyclic)alkoxy,

hydroxy, hydroxalkoxy, phenyl and tetrazolylalkoxy. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group, for example, phenylethenyl and the like.

The term "arylalkoxy" as used herein refers to $R_{45}O$- wherein R_{45} is an arylalkyl group, for example, benzyloxy, and the like.

The term "arylalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group, for example, benzyloxymethyl and the like.

The term "arylalkyl" as used herein refers to an aryl group as previously defined, appended to a loweralkyl radical, for example, benzyl and the like.

The term "aryloxy" as used herein refers to $R_{46}O$- wherein R_{46} is an aryl group, for example, phenoxy, and the like.

The term "arylalkylcarbonyloxy" as used herein refers to a $R_{62}C(O)O$- wherein R_{62} is an arylalkyl group.

The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group.

The term "aryloxyalkyl" refers to an aryloxy group as previously defined appended to an alkyl radical. Examples of aryloxyalkyl include phenoxymethyl, 2-phenoxyethyl and the like.

The term "carboxaldehyde" as used herein refers to a formaldehyde radical, -C(O)H.

The term "carboxamide" as used herein refers to NH_2-C(O)-.

The term "carboxy" as used herein refers to a carboxylic acid radical, -C(O)OH.

The term "carboxyalkenyl" as used herein refers to a carboxy group as previously defined appended to an alkenyl radical as previously defined. Examples of carboxyalkenyl include 2-carboxyethenyl, 3-carboxy-1-propenyl and the like.

The term "carboxyalkoxy" as used herein refers to a carboxy group as previously defined appended to an alkoxy radical as previously defined. Examples of carboxyalkoxy include carboxymethoxy, carboxyethoxy and the like.

The term "cyanoalkoxy" as used herein refers to an alkoxy radical as previously defined to which is appended a cyano (-CN) group. Examples of cyanoalkoxy include 3-cyanopropoxy, 4-cyanobutoxy and the like.

The term "cycloalkanoyloxy" as used herein refers to R_{60}-C(O)-O- wherein R_{60} is a cycloalkyl group.

The term "cycloalkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyloxy group.

The term "cycloalkyl" as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl, and the like. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide.

The term "cycloalkyloxy" herein refers R_{61}-O- wherein R_{61} is a cycloalkyl group. Examples of cycloalkyloxy include cyclohexyloxy and the like.

The term "(cycloalkyl)alkoxy" herein R_{63}-R_{64}-O- wherein R_{63} is a cycloalkyl as defined above and is appended to the parent molecular moiety through an alkoxy radical wherein R_{64} is an alkylene group. Examples of (cycloalkyl)alkoxy include (cyclopropyl)ethoxy and the like.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "dialkylamino" as used herein refers to (R_{56})(R_{57})N- wherein R_{56} and R_{57} are independently selected from loweralkyl, for example diethylamino, methyl propylamino, and the like.

The term "(dialkylamino)alkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group.

The term "(dialkylamino)alkoxy" as used herein refers to an alkoxy radical to which is appended a dialkylamino group.

The term "dialkylaminocarbonyl" as used herein refers to a dialkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of dialkylaminocarbonyl include dimethylaminocarbonyl, diethylaminocarbonyl and the like.

The term "dialkylaminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended a dialkylaminocarbonyl group.

The term "dialkylaminocarbonylalkyl" as used herein refers to R_{58}-C(O)-R_{59}- wherein R_{58} is a dialkylamino group and R_{59} is an alkylene group.

The term "halo" or "halogen" as used herein refers to I, Br, Cl or F.

The term "haloalkenyl" as used herein refers to an alkenyl radical to which is appended at least one halogen substituent.

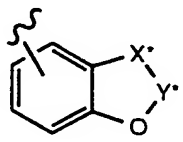
The term "haloalkoxy" as used herein refers to an alkoxy radical as defined above, bearing at least one halogen substituent, for example, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, trifluoromethoxy,

2,2,3,3,3-pentafluoropropoxy and the like.

The term "haloalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended a haloalkoxy group.

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, to which is appended at least one halogen substituent, for example, chloromethyl, fluoroethyl, trifluoromethyl or pentafluoroethyl and the like.

The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; or two sulfur atoms in non-adjacent positions. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The nitrogen heteroatoms can be optionally quaternized. The terms "heterocyclic" or "heterocycle" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cycloalkane ring or another heterocyclic ring (for example, indolyl, dihydroindolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, benzofuryl, dihydrobenzofuryl or benzothienyl and the like). Heterocyclics include: aziridinyl, azetidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, oxetanyl, furyl, tetrahydrofuranyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrimidyl and benzothienyl.

Heterocyclics also include compounds of the formula 

where X* is $-CH_2-$ or -O- and Y* is -C(O)- or $[-C(R")_2-]_v$ where R" is hydrogen or C_1-C_4-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like. Heterocyclics also include bicyclic rings such as quinuclidinyl and the like.

Heterocyclics can be unsubstituted, monosubstituted, disubstituted, or trisubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino,

alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, phenyl, arylalkyl, -COOH, -SO_3H, alkoxycarbonyl, nitro, cyano and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "(heterocyclic)alkoxy" as used herein refers to a heterocyclic group as defined above appended to an alkoxy radical as defined above. Examples of (heterocyclic)alkoxy include 4-pyridylmethoxy, 2-pyridylmethoxy and the like.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above. Examples of (heterocyclic)alkyl include 2-pyridylmethyl and the like.

The term "heterocyclic(amino)" refers to R_{77}-NH- wherein R_{77} is an aromatic heterocyclic group as defined above which is appended to an amino group. The aromatic heterocycle is substituted with substituents R_{75} and R_{76} which are both bonded to the atoms of the aromatic heterocycle which are directly adjacent to the nitrogen. R_{75} and R_{76} are substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, phenyl, arylalkyl, -COOH, -SO_3H, alkoxycarbonyl, nitro, cyano and loweralkyl . The aromatic heterocycle may also be optionally substituted with a third substituent which is selected from the group hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, phenyl, arylalkyl, -COOH, -SO_3H, alkoxycarbonyl, nitro, cyano and loweralkyl. Examples of heterocyclic(amino) include 2,4-diethylpyridine-3-amino, 2,4-diethylthiophene-3-amino, 2,4-diethylpyridine-2-amino, and the like.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to R_{47}-C(O)-O-R_{48}- wherein R_{47} is a heterocyclic group and R_{48} is an alkylene group.

The term "hydroxy" as used herein refers to -OH.

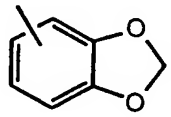
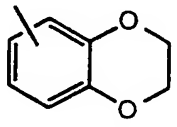
The term "hydroxyalkenyl" as used herein refers to an alkenyl radical to which is appended a hydroxy group.

The term "hydroxyalkoxy" as used herein refers to an alkoxy radical as previously defined to which is appended a hydroxy (-OH) group. Examples of hydroxyalkoxy include 3-hydroxypropoxy, 4-hydroxybutoxy and the like.

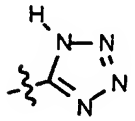
The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended a hydroxy group.

The term "mercapto" as used herein refers to -SH.

The terms "methylenedioxy" and "ethylenedioxy" refer to one or two carbon chains respectively attached to the parent molecular moiety through two oxygen

atoms. In the case of methylenedioxy, a fused 5 membered ring is formed. In the case of ethylenedioxy, a fused 6 membered ring is formed. Methylenedioxy substituted on a phenyl ring results in the formation of a benzodioxolyl radical.  . Ethylenedioxy substituted on a phenyl ring results in the formation of a benzodioxanyl radical  .

The term "substantially pure" as used herein means 90% or more of the specified compound.

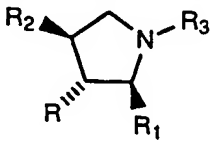
The term "tetrazolyl" as used herein refers to a radical of the formula  or a tautomer thereof.

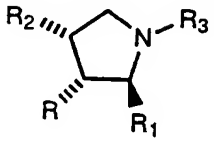
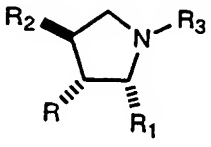
The term "tetrazolylalkoxy" as used herein refers to a tetrazolyl radical as defined above appended to an alkoxy group as defined above. Examples of tetrazolylalkoxy include tetrazolylmethoxy, tetrazolylethoxy and the like.

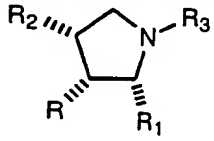
The term "thioalkoxy" as used herein refers to $R_{70}S$- wherein R_{70} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

The term "thioalkoxyalkoxy" as used herein refers to $R_{71}S$-$R_{72}O$- wherein R_{71} is loweralkyl as defined above and R_{72} is alkylene. Representative examples of thioalkoxyalkoxy groups include CH_3SCH_2O-, $CH_3CH_2SCH_2O$-, t-$BuSCH_2O$- and the like.

The term "thioalkoxyalkoxyalkyl" as used herein refers to a thioalkoxyalkoxy group appended to an alkyl radical. Representative examples of thioalkoxyalkoxyalkyl groups include $CH_3SCH_2CH_2OCH_2CH_2$-, $CH_3SCH_2OCH_2$-, and the like.

The term *"trans,trans"* as used herein refers to the orientation of substituents (R_1 and R_2) relative to the central substituent R as shown  .

The term *"trans,cis"* as used herein refers to the orientation of substituents (R_1 and R_2) relative to the central substituent R as shown  or  . This definition encompasses both the case where R and R_2 are *cis* and R and R_1 are *trans* and the case where R_2 and R are *trans* and R and R_1 are *cis*.

The term *"cis,cis"* as used herein refers to the orientation of substituents (R_1 and R_2) relative to the central substituent R as shown 

Representative compounds of the invention include:

trans,trans- 2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-trimethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-trimethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-trimethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(3-Fluoro-4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,

trans,trans-2-(3-methoxy-4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethylphenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethylphenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-dimethylphenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-propoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethylphenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(3-methoxy-4-propoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethylphenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-dibromo)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[*2R,3R,4S*]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-dimethoxy)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((4-bromo-2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2-ethyl-6-methyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-triethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diisopropyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl-4-methyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2*R*,3*R*,4*S*]-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((4-carboxy-2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((4-nitro-2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2-isopropyl-6-methyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2-ethyl-6-methoxy)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-isopropoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(2-fluoro-4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-Ethoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2R,3R,4S]-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2R,3R,4S]-2-(4-(2-Ethoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-isopropoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
or a pharmaceutically acceptable salt thereof.

Preferred compounds of the invention are selected from the group consisting of:
trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
trans,trans-2-(3-Fluoro-4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
trans,trans-2-(3-methoxy-4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
trans,trans-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
trans,trans-2-(4-propoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

trans,trans-2-(3-methoxy-4-propoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
[*2R,3R,4S*]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid; and
[2*R*,3*R*,4*S*]-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-isopropoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(2-fluoro-4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-Ethoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2R,3R,4S]-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2R,3R,4S]-2-(4-(2-Ethoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-isopropoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
or a pharmaceutically acceptable salt thereof.

Most preferred are the compounds:
trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
[*2R,3R,4S*]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
[*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid; and
[2*R*,3*R*,4*S*]-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
trans,trans-2-(4-(2-Methoxyethoxy))-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,

trans,trans-2-(4-(2-Ethoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2R,3R,4S]-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2R,3R,4S]-2-(4-(2-Ethoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-isopropoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
or a pharmaceutically acceptable salt thereof.

Methods for preparing the compounds of the invention are shown in Schemes I-VII.

Scheme I illustrates the general procedure for preparing the compounds of the invention when m is 0 and W is $-CO_2H$. A β-ketoester 1, where E is loweralkyl or a carboxy protecting group, is reacted with a nitro vinyl compound 2, in the presence of a base (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sodium ethoxide or sodium hydride and the like) in an inert solvent such as toluene, benzene, tetrahydrofuran or ethanol and the like. The condensation product 3 is reduced (for example, by hydrogenation using a Raney nickel or platinum catalyst). The resulting amine cyclizes to give the dihydro pyrrole 4. Reduction of 4 (for example, sodium cyanoborohydride or catalytic hydrogenation and the like) in THF solvent or the like gives the pyrrolidine compound 5 as a mixture of *cis-cis*, *trans,trans* and *cis,trans* products. Chromatographic separation removes the *cis-cis* isomer leaving a mixture of the *trans,trans* and *cis,trans* isomers which is further elaborated. The *cis-cis* isomer can be epimerized (for example, using sodium ethoxide in ethanol or DBU in toluene) to give the *trans,trans* isomer and then carried on as described below. The pyrrolidine nitrogen is (1) acylated or sulfonylated with R_3-X (R_3 is R_4-C(O)- or R_6-$S(O)_2$- and X is a leaving group such as a halide (Cl is preferred) or X taken together with R_4-C(O)- or R_6-$S(O)_2$- forms an activated ester including esters or anhydrides derived from formic acid, acetic acid and the like, alkoxycarbonyl halides, N-hydroxysuccinimide, N-hydroxyphthalimide, N-hydroxybenzotriazole, N-hydroxy-5-norbornene-2,3-dicarboxamide, 2,4,5-trichlorophenol and the like) or (2) alkylated with R_3-X where X is a leaving group (for example, X is a halide (for example, Cl, Br or I) or X is a leaving group such as a sulfonate (for example, mesylate, tosylate, triflate and the like)) in the presence of a base such as diisopropyl ethylamine or triethylamine and the like to give the N-derivatized pyrrolidine 6 which is still a mixture of *trans,trans* and *cis,trans* isomers. Hydrolysis of the ester 6 (for example,

using a base such a sodium hydroxide in EtOH/H_2O) selectively hydrolyzes the *trans,trans* ester to give a mixture of 7 and 8, which are readily separated.

Many of the β-ketoester starting materials employed in the preparation of the compounds of the present invention are commercially available. They may also be prepared using the methods indicated in Scheme VIII. In the method of Scheme VIII(a), an aromatic, heteroaromatic, or α- quarternary methyl ketone is deprotonated (e.g., with sodium hydride or lithium diisopropylamide) and treated with a reagent capable of transferring a carboalkoxy group (e.g., diethyl carbonate, methyl chloroformate, or di-tert-butyldicarbonate). Alternatively, as shown in Scheme VIII(b), a carboxylic acid may be activated (e.g., with carbonyldiimidazole or oxalyl chloride) and treated with an acetate equivalent (e.g., ethyl lithioacetate, magnesium methylmalonate, or Meldrum's acid followed by thermal alcoholysis).

A preferred embodiment is shown in Schemes II and III. A benzoyl acetate such as 26 or 4-(2-methoxyethoxy)benzoyl acetate is reacted with a nitro vinyl benzodioxolyl compound 27 using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base in toluene to give compound 28. Catalytic hydrogenation using Raney nickel leads to reduction of the nitro group to an amine and subsequent cyclization to give the dihydropyrrole 29. The double bond is reduced with sodium cyanoborohydride to give the pyrrolidine compound 30 as a mixture of *cis-cis*, *trans,trans* and *cis,trans* isomers. Chromatography separates the *cis-cis* isomer, leaving a mixture of the *trans,trans* and *cis,trans* isomers (31).

Scheme III illustrates the further elaboration of the *trans,trans* isomer. The mixture (31) of *trans,trans* and *cis,trans* pyrrolidines described in Scheme IV is reacted with Br-$CH_2C(O)NHR_4$ in acetonitrile in the presence of ethyldiisopropylamine to give the alkylated pyrrolidine compound 32, still as a mixture of *trans,trans* and *cis,trans* isomers. Sodium hydroxide in ethanol-water hydrolyzes the ethyl ester of the *trans,trans* compound but leaves the ethyl ester of the cis,trans compound untouched, thus allowing separation of the *trans,trans* carboxylic acid 33 from the *cis,trans* ester 34.

Scheme IV illustrates the preparation of compounds where W is other than carboxylic acid. Compound 55, which can be prepared by the procedures described in Scheme I, is converted (for example, using peptide coupling condition, e.g. N-methylmorpholine, EDCI and HOBt, in the presence of ammonia or other amide forming reactions) to give carboxamide 56. The carboxamide is dehydrated (for example, using phosphorus oxychloride in pyridine) to give nitrile 57. Nitrile 57 under standard tetrazole-forming conditions (sodium azide and triethylamine

hydrochloride or trimethylsilylazide and tin oxide) is reacted to give tetrazole 58. Alternatively nitrile 57 is reacted with hydroxylamine hydrochloride in the presence of a base (for example, potassium carbonate, sodium carbonate, sodium hydroxide, triethylamine, sodium methoxide or NaH) in a solvent such as DMF, DMSO, or dimethylacetamide to give amidoxime 59. The amidoxime 59 is allowed to react with a methyl or ethyl chloroformate in a conventional organic solvent (such as, chloroform, methylene chloride, dioxane, THF, acetonitrile or pyridine) in the presence of a base (for example, triethylamine, pyridine, potassium carbonate and sodium carbonate) to give an O-acyl compound. Heating of the O-acyl amidoxime in an inert solvent (such as benzene, toluene, xylene, dioxane, THF, dichloroethane, or chloroform and the like) results in cyclization to compound 60. Alternatively reacting the amidoxime 59 with thionyl chloride in an inert solvent (for example, chloroform, dichloromethane, dioxane and THF and the like) affords the oxathiadiazole 61.

Scheme V illustrates a method for synthesizing pyrrolidines by an azomethine ylide type [3+2]-cycloaddition to an acrylate. General structures such as compound 70 are known to add to unsaturated esters such as 71 to provide pyrrolidines such as compound 72 (O. Tsuge, S. Kanemasa, K. Matsuda, Chem. Lett. 1131-4 (1983), O. Tsuge, S. Kanemasa, T. Yamada, K. Matsuda, J. Org. Chem. 52 2523-30 (1987), and S. Kanemasa, K. Skamoto, O. Tsuge, Bull. Chem. Soc. Jpn. 62 1960-68 (1989)). Silylimine 73 is reacted with acrylate 74 in the presence of trimethylsilyl triflate and tetrabutylammonium fluoride to give the desired pyrrolidine 75 as a mixture of isomers. This method can be modified to provide the N-acetamido derivatives directly by reacting 73 and 74 with the appropriate bromoacetamide (for example, dibutyl bromoacetamide) in the presence of tetrabutylammonium iodide and cesium fluoride to give compound 76.

Scheme VI illustrates a method for producing an enantiomerically pure pyrrolidine 80, which can be further elaborated on the pyrrolidine nitrogen. Intermediate racemic pyrrolidine ester 77 (for example, prepared by the procedure described in Scheme V) is Boc-nitrogen protected (for example, by treatment with Boc_2O) and then the ester is hydrolyzed (for example, using sodium or lithium hydroxide in ethanol and water) to give t-butyl carbamoyl pyrrolidine carboxylic acid 78. The carboxylic acid is converted to its (+)-α-methylbenzylamine salt, which can be recrystallized (for example from ethyl acetate and hexane or chloroform and hexane) to afford the diastereomerically pure salt. This diastereomerically pure salt can be neutralized (for example, with sodium carbonate or citric acid) to afford enantiomerically pure carboxylic acid 79. The pyrrolidine nitrogen can be deprotected (for example, using trifluoroacetic acid) and the ester reformed by the

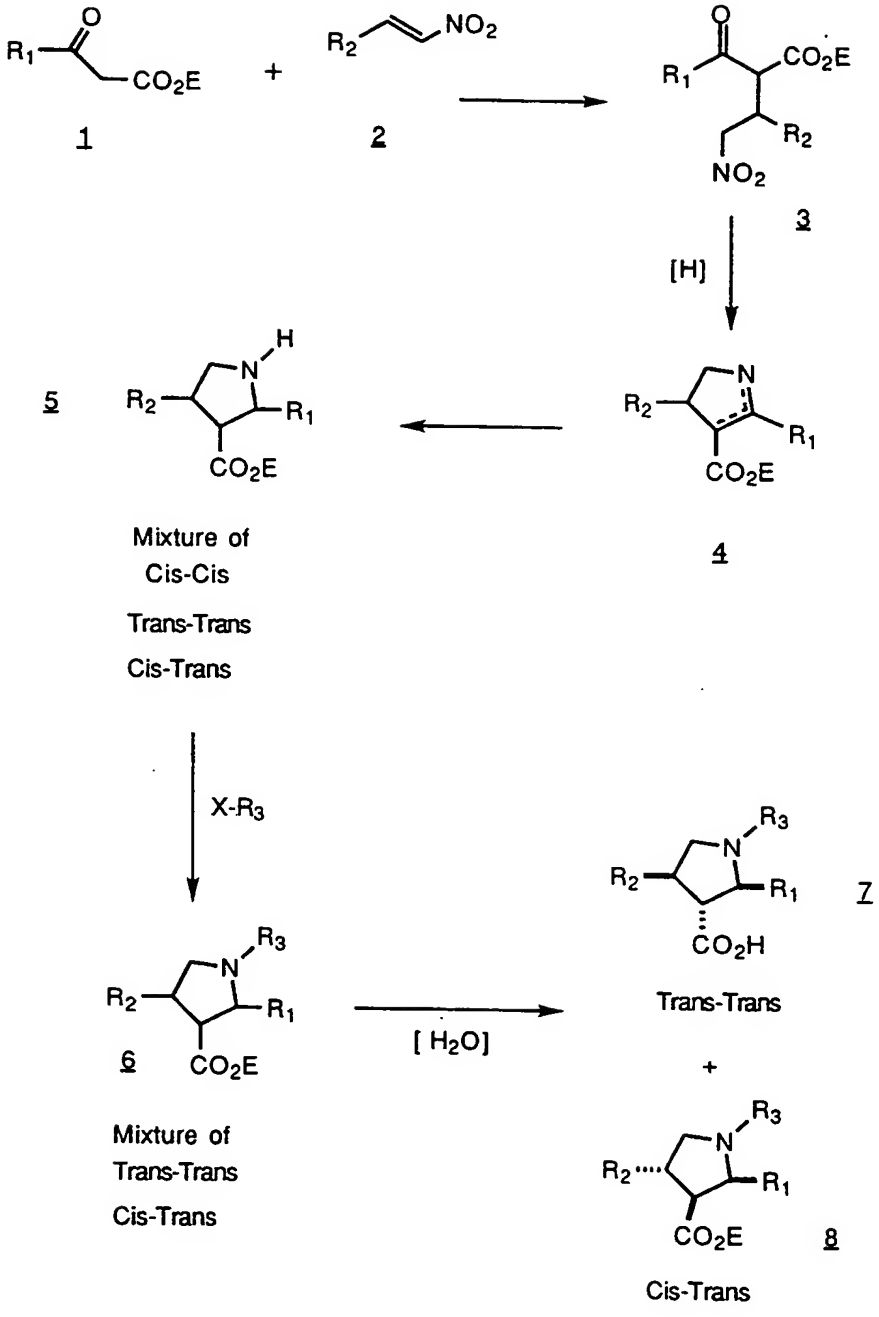
use of ethanolic hydrochloric acid to give salt 80. Alternatively one can use ethanolic HCl to cleave the protecting group and form the ester in one step. The pyrrolidine nitrogen can be further elaborated (for example, by treatment with the 2,6-diethylbenzamide of bromoacetic acid in acetonitrile in the presence of diisopropylethylamine) to give optically active compound 81. The use of (-)-α-methylbenzylamine will give the opposite enantiomer. Other optically active amines may also be employed.

A preferred process is shown in Scheme VII. Nitro vinyl compound (88) is reacted with β-keto ester 89 in the presence of a base such as sodium ethoxide and the like or a trialkylamine such as triethylamine or diisopropylethylamine and the like or an amidine such as DBU and the like in an inert solvent such as THF, toluene, DMF, acetonitrile, ethyl acetate, isopropyl acetate or methylene chloride and the like at a temperature of from about 0° C to about 100° C for a period of time from about 15 minutes to overnight to give compound 90. Reduction of the nitro group followed by cyclization was effected for example by catalytic hydrogenation with a hydrogen pressure of from about atmospheric pressure to 300 p.s.i. over from about 1 hour to about 1 day of compound 90 in an inert solvent such as THF, ethyl acetate, toluene, ethanol, isopropanol, DMF or acetonitrile and the like, using a hydrogenation catalyst such as Raney nickel, palladium on carbon, a platinum catalyst, such as platinum oxide, platinum on carbon or platinum on alumina and the like, or a rhodium catalyst, such as rhodium on carbon or rhodium on alumina and the like, and the like affords intermediate nitrone 91a or a mixture of nitrone 91a and imine 91b. The reaction mixture comprising the nitrone or nitrone/imine mixture is treated with an acid such as trifluoroacetic acid or acetic acid or sulfuric acid or phosphoric acid or methanesulfonic acid and the like, and the hydrogenation is continued to give pyrrolidine compound 92 as the cis,cis-isomer. Epimerization at C-3 is effected by treatment of compound 92 with a base such as sodium ethoxide, potassium t-butoxide, lithium t-butoxide or potassium t-amyloxide and the like or a trialkylamine such as triethylamine or diisopropylethylamine and the like or an amidine such as DBU and the like in an inert solvent such as ethanol, ethyl acetate, isopropyl acetate, THF, toluene or DMF and the like at a temperature of from about -20° C to about 120° C to give the trans,trans compound 93. Compound 93 itself can optionally be resolved into enantiomers prior to reacting with X-R_3. The substantially pure (i.e., at least 95% of the desired isomer) optically active (+)-isomer of compound 93 is obtained by treatment of a mixture of the (+)-isomer and the (-)-isomer of 93 with S-(+)-mandelic acid, D-tartaric acid or D-dibenzoyl tartaric acid or the like in a solvent such as acetonitrile, ethyl acetate, isopropyl acetate, ethanol or isopropanol and the

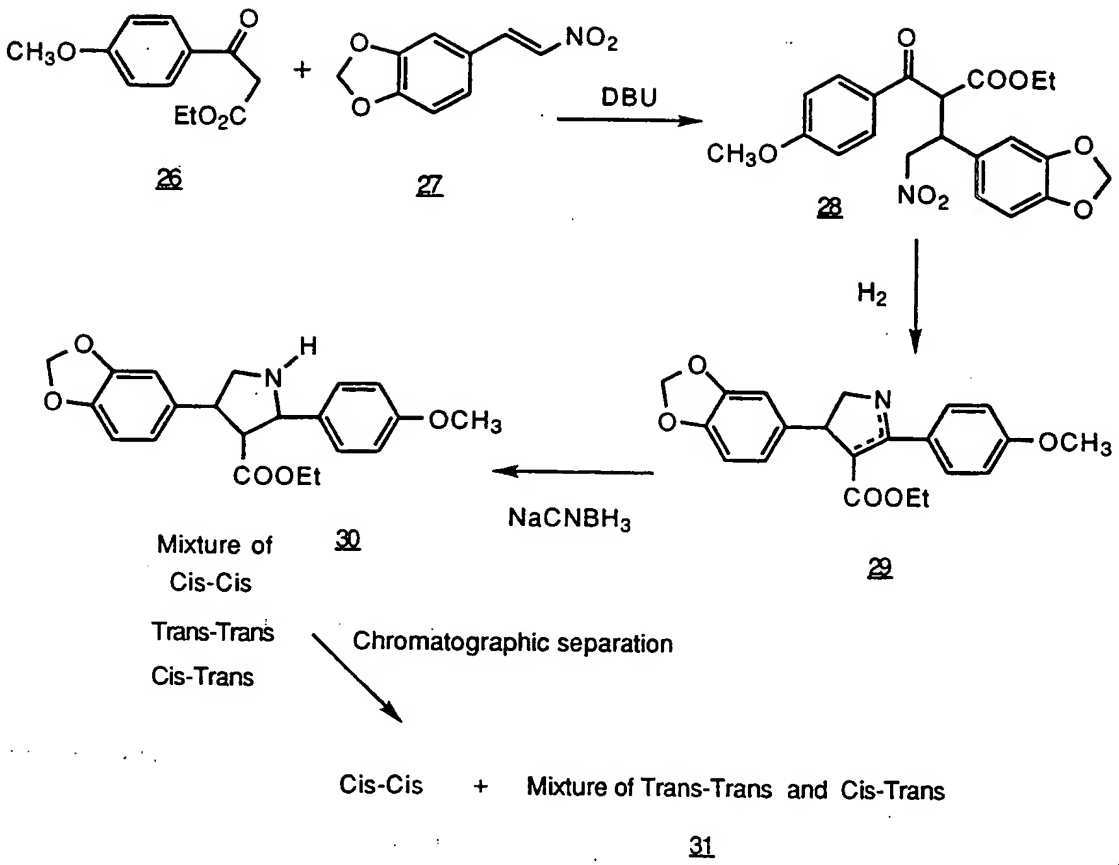
like. The (+)-isomer of 93 selectively crystallizes as the salt, leaving the (-)-isomer of 93 in solution. Alternatively, the substantially pure (i.e., at least 95% of the desired isomer) optically active (-)-isomer of compound 93 can be selectively crystallized by reaction of a mixture of the (+)-isomer and the (-)-isomer of 93 with L-tartaric acid, L-dibenzoyl tartaric acid or L-pyroglutamic acid and the like, leaving the desired (+)-isomer of compound 93 in solution.

Compound 93 (racemic or optically active) is reacted with X-R_3 (where X is a leaving group (for example, a halide or a sulfonate) and R_3 is as previously defined) using a base such as diisopropylethylamine, triethylamine, sodium bicarbonate or potassium carbonate and the like in an inert solvent such as acetonitrile, THF, toluene, DMF or ethanol and the like at a temperature of from about 0° C to about 100° C to give the intermediate ester 94. The ester can be isolated or converted *in situ* to the carboxylic acid (95) using hydrolysis conditions such as a base such as sodium hydroxide or lithium hydroxide or potassium hydroxide and the like in a solvent such as ethanol-water or THF-ethanol and the like.

Scheme I


R1
O
CO2E
1
+
R2
NO2
2
R1
O
CO2E
R2
NO2
3
[H]
R2
N
R1
CO2E
4
5
R2
N
H
R1
CO2E
Mixture of
Cis-Cis
Trans-Trans
Cis-Trans
X-R3
R2
N
R3
R1
CO2E
6
Mixture of
Trans-Trans
Cis-Trans
[H2O]
R2
N
R3
R1
CO2H
7
Trans-Trans
+
R2
N
R3
R1
CO2E
8
Cis-Trans

Scheme II

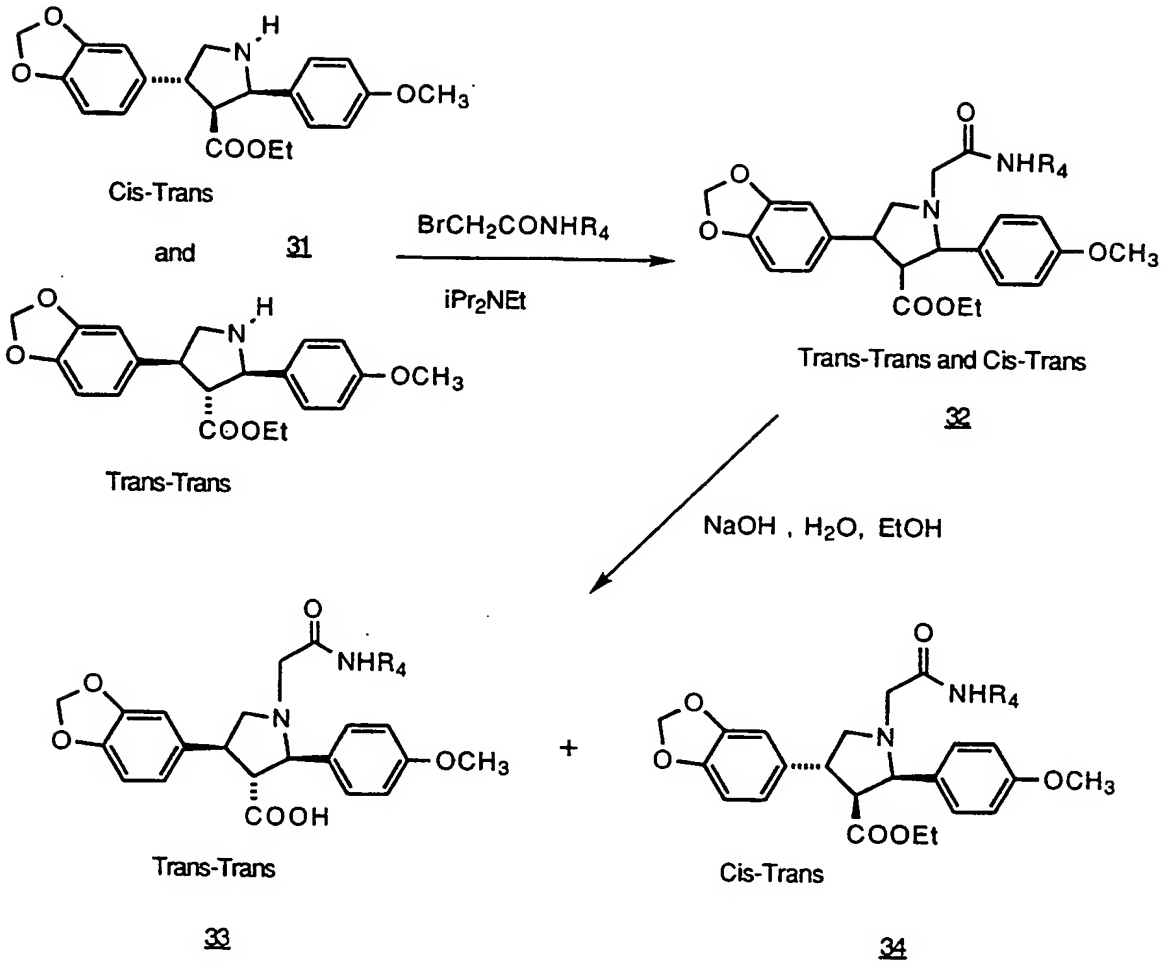


26 27 28 29 30

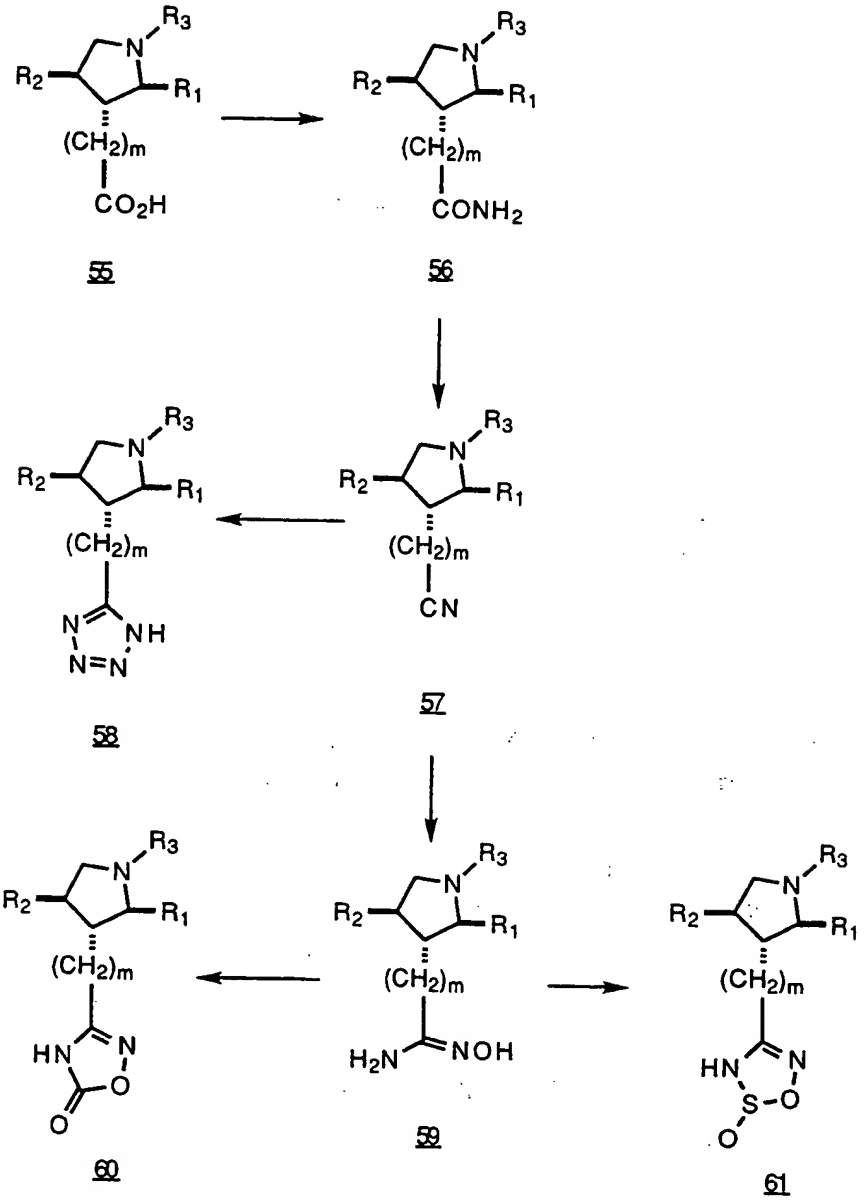
Cis-Cis + Mixture of Trans-Trans and Cis-Trans

31

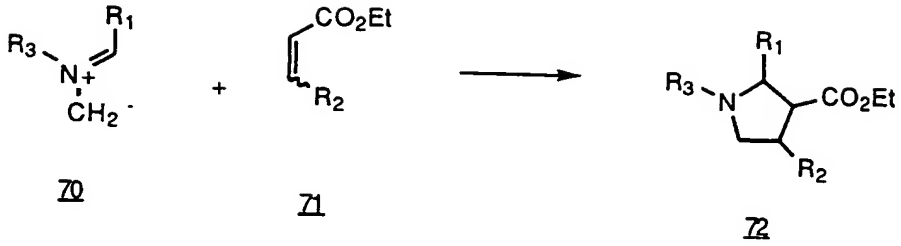
Scheme III


Cis-Trans
and
31
Trans-Trans
BrCH2CONHR4
iPr2NEt
Trans-Trans and Cis-Trans
32
NaOH , H2O, EtOH
Trans-Trans
33
+
Cis-Trans
34

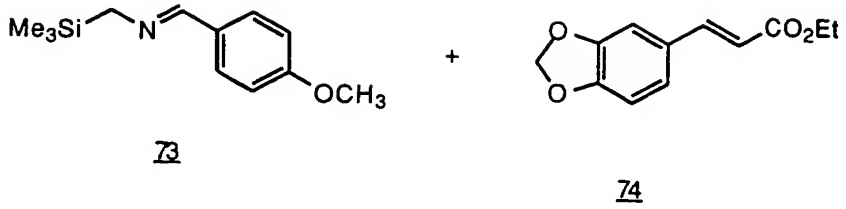
Scheme IV


R3
N
R2
R1
(CH2)m
CO2H
55
CONH2
56
CN
57
NH
N=N
58
NOH
H2N
59
HN
O
60
S
61

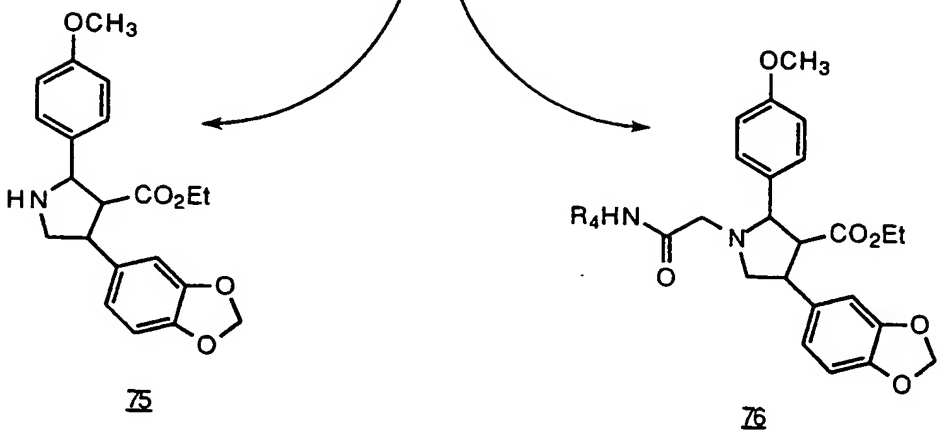
Scheme V



70 71 72

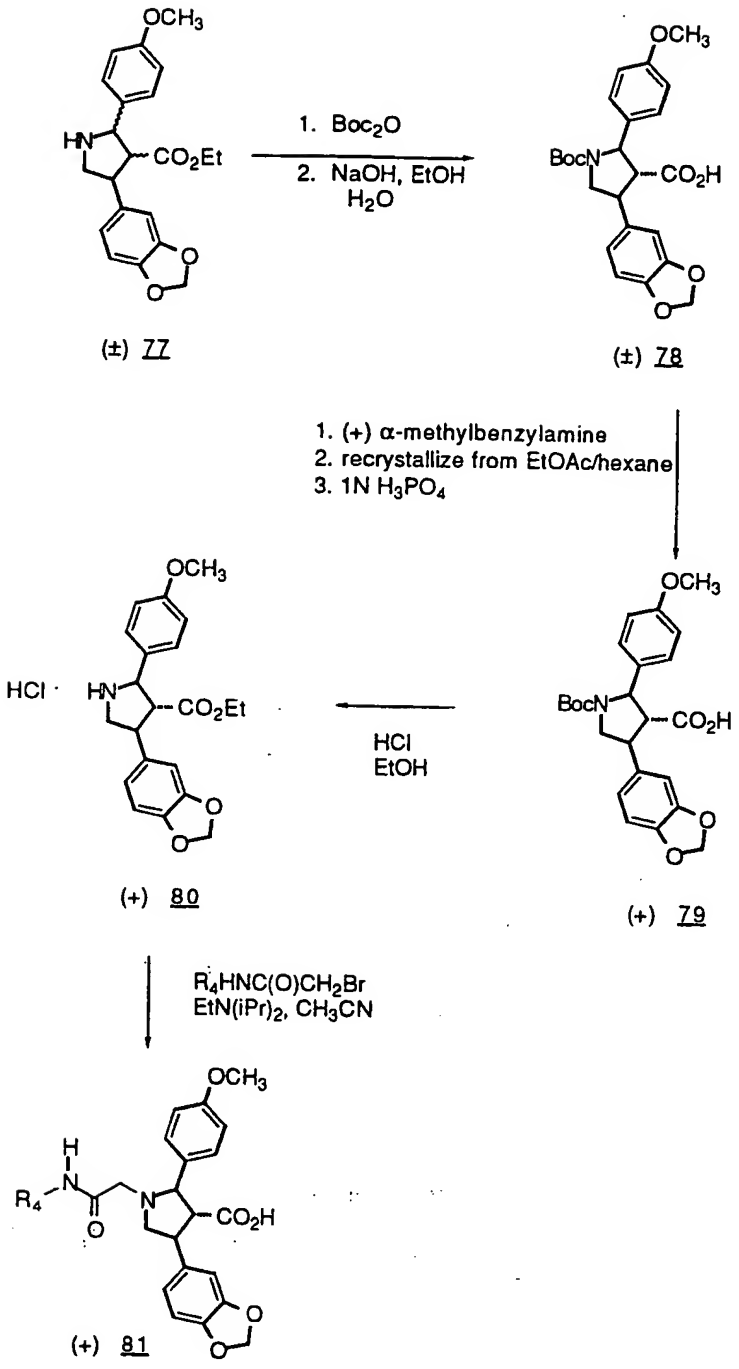


73 74

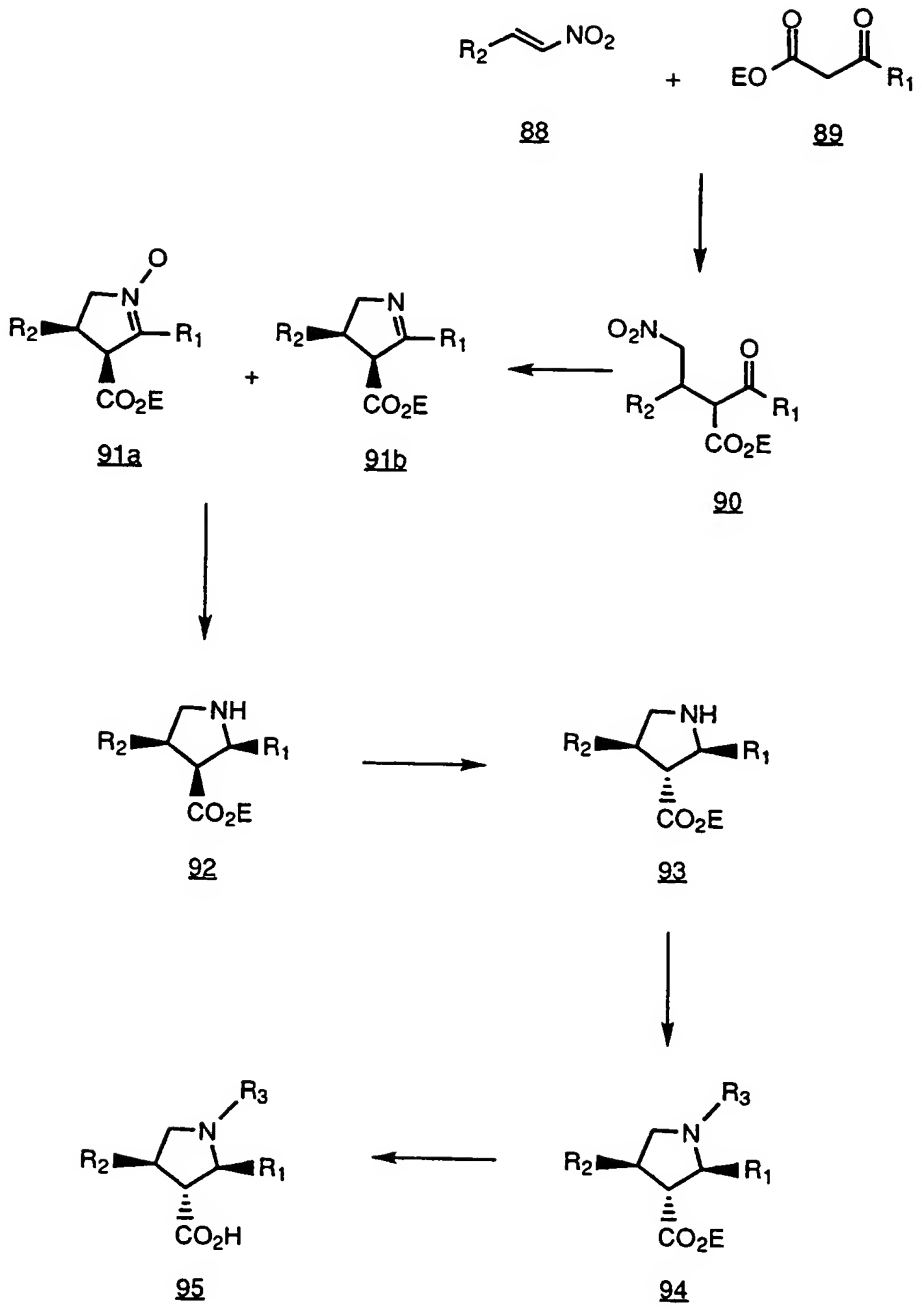


75 76

Scheme VI

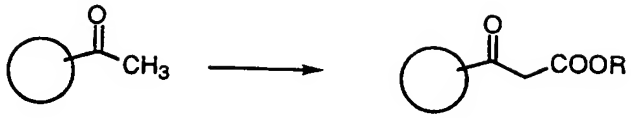

OCH3
HN
CO2Et
1. Boc2O
2. NaOH, EtOH
H2O
BocN
CO2H
(±) 77
(±) 78
1. (+) α-methylbenzylamine
2. recrystallize from EtOAc/hexane
3. 1N H3PO4
HCl ·
HCl
EtOH
(+) 80
(+) 79
R4HNC(O)CH2Br
EtN(iPr)2, CH3CN
R4
(+) 81

Scheme VII


R2
NO2
88
+
EO
O
O
R1
89
O2N
R2
R1
CO2E
90
N
O
91a
91b
NH
92
93
R3
CO2H
95
94

SCHEMEVIII.

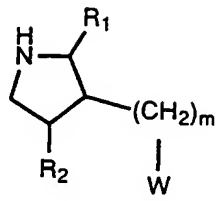
Scheme VIIIa.



Aryl, Heteroaryl, or
α-quarternary

Scheme VIIIb.

Compounds which are useful as intermediates for the preparation of compounds of the invention are:



(III)

wherein

m is 0 to 6;

W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group, (b) $-PO_3H_2$,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

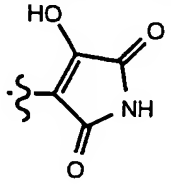
(i) hydroxy,

(j) alkoxy,

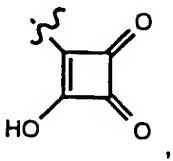
(k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,

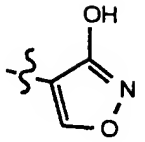
(m) $-S(O)_2NHC(O)R_{16}$,

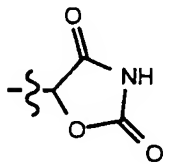


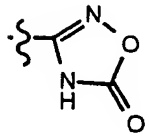
(n),

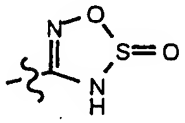


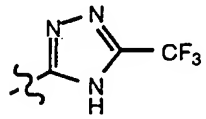
(o),

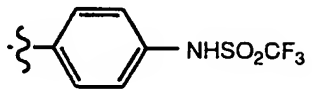
(p)  ,

(q)  ,

(r)  ,

(s)  ,

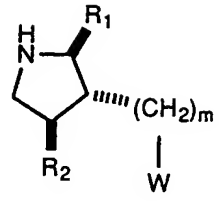
(t)  , or

(u)  ; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N\text{-}R_{cc}$- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

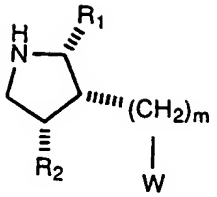
or a salt thereof;

and a compound of the formula:



(IV)

or



(V)

wherein n is 0 or 1;

m is 0 to 6;

W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

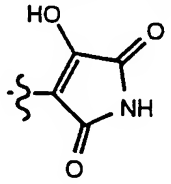
(i) hydroxy,

(j) alkoxy,

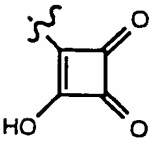
(k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,

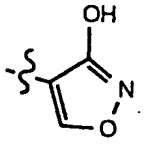
(m) $-S(O)_2NHC(O)R_{16}$,



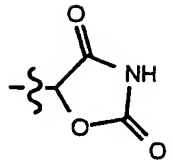
(n) ,

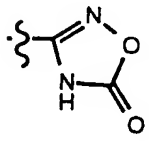


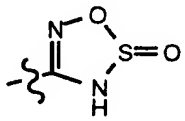
(o) ,

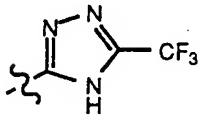


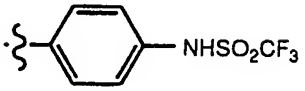
(p) ,

(q)  ,

(r)  ,

(s)  ,

(t)  , or

(u)  ; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N\text{-}R_{cc}$- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen; or a salt thereof.

Preferred intermediates include compounds of formula (III), (IV) and (V) wherein

m is zero or 1;

W is $-CO_2$-G wherein G is hydrogen or a carboxy protecting group, and R_1 and R_2 are as defined above; or

the substantially pure (+)- or (-)-isomer thereof.

Particularly preferred intermediates are compounds of formula (III), (IV) and (V) wherein

m is 0;

W is $-CO_2$-G wherein G is hydrogen or a carboxy protecting group;

and R_1 is (i) alkoxyalkylalkyl, (ii) cycloalkyl, (iii) phenyl, (iv) pyridyl, (v) furanyl or (vi) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-trifluoromethylphenyl, 4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy and R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl; or
the substantially pure (+)- or (-)-isomer thereof.

The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept. The following abbreviations are used: Boc for tert-butyloxycarbonyl, Cbz for benzyloxycarbonyl, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, EDCI for 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride, EtOAc for ethyl acetate, EtOH for ethanol, HOBt for 1-hydroxybenzotriazole, Et_3N for triethylamine, TFA for trifluoroacetic acid and THF for tetrahydrofuran.

Example 1

trans,trans- 2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-trimethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 1A

Ethyl 2-(4-methoxybenzoyl)-4-nitromethyl-3-(1,3-benzodioxole-5-yl)butyrate

To ethyl (4-methoxybenzoyl)acetate (23.0 g, 0.104 mol), prepared by the method of Krapcho *et al.*, Org. Syn. 47, 20 (1967), and 5-(2-nitrovinyl)-1,3-benzodioxole (17.0 g, 0.088 mol) dissolved in 180 mL of toluene and heated to 80 °C was added 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU, 0.65 g) with stirring. The mixture was heated until all the nitro starting material dissolved. The solution was stirred without heating for 30 minutes and then an additional 0.65 g of DBU was added. After stirring an additional 45 minutes, thin layer chromatography (5% ethyl acetate in methylene chloride) indicated the absence of nitro starting material. Toluene (200 mL) was added, and the organic phase was washed with dilute

hydrochloric acid and NaCl solution. The organic phase was dried over sodium sulfate and then concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 3:1 hexane-ethyl acetate to give 21.22 g of the desired product as a mixture of isomers and 9.98 g. of recovered ethyl (4-methoxybenzoyl)acetate.

Example 1B

Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-4,5-dihydro-3H-pyrrole-3-carboxylate

The compound resulting from Example 1A (21 g) in 500 mL of ethanol was hydrogenated under 4 atmospheres of hydrogen pressure using a Raney nickel 2800 catalyst (51 g). (The Raney nickel was washed with ethanol three times before use.) The catalyst was removed by filtration, and the solution was concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 8.5% ethyl acetate in methylene chloride to give 12.34 g of the desired product.

Example 1C

Ethyl 2-(4-methoxyphenyl-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate) as a mixture of *cis-cis*; *trans,trans*; and *cis,trans*-isomers

The compound resulting from Example 1B (11.89 g, 0.324 mol) was dissolved in 27 mL of tetrahydrofuran and 54 mL of ethanol. Sodium cyanoborohydride (2.35 g, 0.374 mol) and 5 mg bromocresol green were added. To this blue solution was added dropwise a solution of 1:2 concentrated HCl in ethanol at such a rate that the color was kept at light yellow-green. After the yellow color persisted without additional HCl, the solution was stirred an additional 20 minutes. The solution was concentrated *in vacuo* and then partitioned between chloroform and an aqueous potassium bicarbonate solution. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 85:15 ethyl acetate-hexane to give 5.96 g. of a mixture of 64% *trans,trans*-compound and 34% *cis,trans*-compound. Further elution with pure ethyl acetate gave 0.505 g of an unknown solid followed by 3.044 g of pure *cis,cis*-compound.

Example 1D

N-(2,4,6-Trimethylphenyl) bromoacetamide

To a stirred solution of 2,4,6-trimethylaniline (1 g, 7.40 mmol) in methylene chloride (25 mL) at -50 °C was added successively *N,N*-diisopropylethylamine (1.58

mL, 8.14 mmol, 1.1 eq) and bromoacetyl bromide (0.72 mL, 7.40 mmol, 1 eq) such that the temperature did not exceed -40 °C. On completion of the addition, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After stirring for a further 30 minutes, the mixture was diluted with ether (70 mL) and poured into 1 N sodium bisulfate solution. The phases were separated, and the upper layer was washed successively with water and brine. The organic phase was dried (Na_2SO_4) and the solvent evaporated to half volume, at which point the product crystallized. The crystals were removed by vacuum filtration to afford the title compound (1.51 g, 80%).

Example 1E

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-trimethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The mixture of 64% *trans,trans*- and 34% *cis,trans*-pyrrolidines (the mixture resulting from Example 1C) (5.72 g, 15.50 mmol), ethyldiisopropylamine (4.20 g, 32.56 mmol), and the compound resulting from Example 1D (19.0 mmol) in 30 mL of acetonitrile was heated at 50 °C for 1 hour. The solution was concentrated *in vacuo*. The residue was dissolved in toluene, shaken with potassium bicarbonate solution, dried over sodium sulfate and concentrated *in vacuo* to give the product as a mixture of *trans,trans*- and *cis,trans*- ethyl esters.

This mixture was dissolved in a solution of 50 mL of ethanol and 15 mL of water containing 5.00 g of sodium hydroxide and stirred for 3 hours at room temperature. The solution was concentrated *in vacuo* and 60 mL of water added. The mixture was extracted with ether to remove the unreacted *cis,trans*- ethyl ester. The aqueous phase was treated with hydrochloric acid until slightly cloudy. It was then further neutralized with acetic acid to give the crude acid product. The crude product was filtered and purified by dissolving it in tetrahydrofuran, drying over sodium sulfate, concentrating *in vacuo*, and crystallizing from ether to give the title compound. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.22 (1H, bs), 7.78 (2H, d, *J*=8Hz), 6.95 (5H, m), 6.82 (1H, bd, *J*=8Hz), 6.77 (1H, d, *J*=8Hz), 5.96 (2H, s), 3.97 (1H, bd, *J*=10Hz), 3.81 (3H, s), 3.70 (1H, ddd, 6, 5&3Hz), 3.57 (bdd, 10&3Hz), 3.45 (1H, d, *J*=16Hz), 3.13 (2H, m), 2.24 (3H, s), 2.06 (6H, s). MS (DCI, NH_3) m/e 517 ($M+H^+$). Anal. Calc for $C_{30}H_{32}N_2O_6 \cdot 0.5H_2O$: C, 68.56, H, 6.33, N 5.33. Found: C, 68.84, H, 6.20, N, 5.31

Example 2

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-trimethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.22 (1H, bs), 7.21 (1H, dd, *J*=12&2Hz), 7.12 (1H, bd, *J*=8Hz), 6.95 (1H, t, 8Hz), 6.90 (2H, bs), 6.84 (1H, d, *J*=2Hz), 6.80 (1H, dd, *J*=8&3Hz), 6.76 (1H, d, *J*=8Hz), 5.93 (2H, s), 3.96 (1H, d, *J*=10Hz), 3.89 (3H, s), 3.70 (1H, ddd, 6, 5&3Hz), 3.56 (1H, dd, 11&5Hz), 3.45 (1H, d, *J*=16Hz), 3.10 (1H, t, *J*=10Hz), 3.07 (1H, dd, 8&6Hz), 3.02 (1H, d, *J*=16Hz), 2.17 (3H, s), 2.07 (6H, s). MS (DCI, NH_3) m/e 535 (M+H$^+$). Anal. Calc for $C_{30}H_{31}FN_2O_6 \cdot 0.75H_2O$: C, 65.74, H, 5.98, N 5.11. Found: C, 65.96, H, 5.88, N, 5.16

Example 3

trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-trimethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.21 (1H, bs), 7.38 (2H, d, *J*=8Hz), 6.90 (2H, d, *J*=8Hz), 6.89 (2H, d, 3Hz), 7.83 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=8Hz), 5.94 (1H, d, *J*=3Hz), 5.93 (1H, d, *J*=3Hz), 3.96 (1H, d, *J*=10Hz), 3.85 (2H, q, *J*=7Hz), 3.70 (1H, ddd, 6, 5&3Hz), 3.58 (1H, dd, 11&5Hz), 3.48 (1H, d, *J*=16Hz), 3.15 (1H, dd, 8&6Hz), 3.13 (1H, t, *J*=10Hz), 2.99 (1H, d, *J*=16Hz), 2.25 (3H, s), 2.05 (6H, s), 1.81 (2H, sext, *J*=7Hz), 1.04 (3H, t, *J*=7Hz). MS (DCI, NH_3) m/e 545 (M+H$^+$). Anal. Calc for $C_{32}H_{36}N_2O_6 \cdot 0.33H_2O$: C, 69.79, H, 6.71, N 5.09, Found: C, 69.78, H, 6.73, N, 4.81

Example 4

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.24 (1H, bs), 7.39 (2H, d, *J*=8Hz), 7.21 (1H, dd, 8&6Hz), 7.11 (2H, d, *J*=8Hz), 6.92 (2H, d, 8Hz), 7.89 (1H, d, *J*=3Hz), 7.82 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=8Hz), 5.94 (1H, d, *J*=3Hz), 5.93 (1H, d, *J*=3Hz), 3.96 (1H, d, *J*=10Hz), 3.82 (3H, s), 3.70 (1H, ddd, 6, 5&3Hz), 3.56 (1H, dd, 11&5Hz), 3.45 (1H, d, *J*=16Hz), 3.15 (1H, dd, 8&6Hz), 3.13 (1H, t, *J*=10Hz), 3.01 (1H, d, *J*=16Hz), 2.42 (4H, q, *J*=7Hz), 1.08 (6H, t, *J*=7Hz). MS (DCI, NH_3) m/e 559 (M+H_4^+), 531 (M+H$^+$). Anal. Calc for $C_{31}H_{34}N_2O_6$: C, 70.17, H, 6.46, N 5.28. Found: C, 69.88, H, 6.42, N, 5.09.

Example 5

trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.27 (1H, bs), 7.37 (2H, d, *J*=8Hz), 7.21 (1H, dd, 8&6Hz), 7.11 (2H, d, *J*=8Hz), 6.90 (2H, d, 8Hz), 7.86 (1H, d, *J*=3Hz), 7.83 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=8Hz), 5.93 (1H, d, *J*=3Hz), 5.92 (1H, d, *J*=3Hz), 3.96 (1H, d, *J*=10Hz), 3.85 (2H, q, *J*=7Hz), 3.70 (1H, ddd, 6, 5&3Hz), 3.55 (1H, dd, 11&5Hz), 3.48 (1H, d, *J*=16Hz), 3.15 (1H, dd, 8&6Hz), 3.13 (1H, t, *J*=10Hz), 3.01 (1H, d, *J*=16Hz), 2.43 (4H, q, *J*=7Hz), 1.82 (2H, sext, *J*=7Hz), 1.08 (6H, t, *J*=7Hz) 1.04 (3H, t, *J*=7Hz). MS (DCI, NH_3) m/e 559 ($M+H^+$). Anal. Calc for $C_{33}H_{38}N_2O_6 \cdot 0.25H_2O$: C, 70.38, H, 6.89, N 4.97. Found: C, 70.49, H, 6.85, N, 4.68.

Example 6

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.21 (1H, bs), 7.22 (1H, dt, *J*=8&2Hz), 7.20 (1H, d, *J*=8Hz), 7.17 (1H, dt, *J*=8&2Hz), 7.10 (2H, d, *J*=8Hz), 6.96 (1H, t, *J*=8Hz), 6.83 (1H, dd, *J*=8&2Hz), 6.80 (1H, d, *J*=3Hz), 6.76 (1H, d, *J*=8Hz), 5.94 (1H, d, *J*=3Hz), 5.93 (1H, d, *J*=3Hz), 3.97 (1H, d, *J*=10Hz), 3.90 (3H, s), 3.72 (1H, ddd, 6, 5&3Hz), 3.58 (1H, dd, 11&5Hz), 3.46 (1H, d, *J*=16Hz), 3.14 (1H, t, *J*=10Hz), 3.12 (1H, dd, 8&6Hz), 3.05 (1H, d, *J*=16Hz), 2.45 (4H, q, *J*=7Hz), 1.09 (6H, t, *J*=7Hz). MS (DCI, NH_3) m/e 549 ($M+H^+$). Anal. Calc for $C_{31}H_{33}FN_2O_6 \cdot 0.5H_2O$: C, 66.78, H, 6.15, N 5.02. Found: C, 66.81, H, 5.89, N, 4.87.

Example 7

trans,trans-2-(3-Fluoro-4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.23 (1H, bs), 7.23 (1H, d, *J*=2Hz), 7.20 (1H, dd, *J*=8&3Hz), 7.11 (3H, m), 6.96 (1H, t, *J*=8Hz), 6.83 (1H, dd, *J*=8&2Hz), 6.80 (1H, d, *J*=3Hz), 6.76 (1H, d, *J*=8Hz), 5.93 (1H, d, *J*=3Hz), 5.92 (1H, d, *J*=3Hz), 4.11 (2H, t. *J*=7Hz), 3.97 (1H, d, *J*=10Hz), 3.72 (1H, ddd, 6, 5&3Hz), 3.55 (1H, dd, 11&5Hz), 3.47 (1H, d, *J*=16Hz), 3.14 (1H, t, *J*=10Hz), 3.12 (1H, dd, 8&6Hz), 3.04 (1H, d, *J*=16Hz), 2.45 (4H, q, *J*=7Hz), 1.47 (3H, t, *J*=7Hz), 1.09 (6H, t, *J*=7Hz). MS (DCI, NH_3) m/e 563

(M+H+). Anal. Calc for $C_{32}H_{35}FN_2O_6 \cdot 0.15TFA$: C, 66.92, H, 6.11, N 4.83. Found: C, 67.19, H, 5.75, N, 4.69.

Example 8

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.24 (1H, s), 7.25 (1H, t, *J*=3Hz), 7.21 (1H, bd), 7.14 (1H, m), 7.08 (2H, d, *J*=8Hz), 6.96 (1H, t, *J*=8Hz), 6.56 (1H, d, *J*=3Hz), 6.50 (1H, d, *J*=3Hz), 5.93 (1H, d, *J*=2Hz), 5.91 (1H, d, *J*=2Hz), 3.97 (1H, d, *J*=10Hz), 3.90 (3H, s), 3.72 (1H, ddd, 6, 5&3Hz), 3.58 (1H, dd, 11&5Hz), 3.46 (1H, d, *J*=16Hz), 3.14 (1H, t, *J*=10Hz), 3.12 (1H, dd, 8&6Hz), 3.05 (1H, d, *J*=16Hz), 2.45 (4H, q, *J*=7Hz), 1.09 (6H, t, *J*=7Hz). MS (DCI, NH_3) m/e 579 ($M+H^+$). Anal. calcd for $C_{32}H_{35}FN_2O_7 \cdot 1.5H_2O$: C, 63.65, H, 6.31, N 4.64. Found: C, 64.00, H, 6.29, N, 4.26.

Example 9

trans,trans-2-(3-methoxy-4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.22 (1H, s), 7.21 (1H, m), 7.12 (2H, d, *J*=10Hz), 7.02 (1H, dd, *J*=9&3Hz), 6.93 (1H, d, *J*=2Hz), 6.88 (1H, d, *J*=2Hz), 6.85 (1H, m), 6.82 (1H, d, *J*=2Hz), 6.75 (1H, d, *J*=9Hz), 5.95 (1H, d, *J*=2Hz), 5.93 (1H, d, *J*=2Hz), 3.97 (2H, q, *J*=9Hz), 3.84 (3H, s), 3.72 (2H, m), 3.60-3.45 (2H, m), 3.15 (2H, m), 3.03 (1H, d *J*=18Hz), 2.43 (4H, q, *J*=9Hz), 1.87 (2H, m), 1.08 (6H, t, *J*=9Hz), 1.04 (3H, t, *J*=9Hz). MS (DCI, NH_3) m/e 589 (MH^+). Anal.calcd. for $C_{34}H_{40}N_2O_7 \cdot 0.45\ H_2O$: C, 68.43, H, 6.91, N, 4.69. Found: C, 68.45, H, 6.91, N, 4.62.

Example 10

trans,trans-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.26 (1H, bs), 7.36 (2H, d, *J*=9Hz), 7.21 (1H, m), 7.11 (2H, d, *J*=10Hz), 6.90 (2H, d, *J*=9Hz), 6.86 (1H, d, *J*=2Hz), 6.83 (1H, dd, *J*=8&2Hz), 6.73 (1H, d, *J*=9Hz), 5.94 (1H, d, *J*=2Hz), 5.92 (1H, d, *J*=2Hz), 4.10-3.90 (3H, m), 3.71

(1H, m), 3.60-3.40 (2H, m), 3.15 (2H, m), 3.02 (1H, d *J*=18Hz), 2.43 (4H, q, *J*=9Hz), 1.42 (3H, t, *J*=9Hz), 1.08 (6H, t, *J*=9Hz). MS (DCI, NH_3) m/e 545 (MH^+). Anal. calcd. for $C_{32}H_{36}N_2O_6 \cdot 0.5\ H_2O$: C, 69.42, H, 6.74, N, 5.06. Found: C, 69.52, H, 6.52, N, 4.89.

Example 11

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-dimethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, $CDCl_3$) δ 8.32 (1H, bs), 7.37 (2H, d, *J*=9Hz), 7.08 (3H, m), 6.91 (2H, d, *J*=9Hz), 6.88 (1H, d, *J*=2Hz), 6.82 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=9Hz), 5.95 (1H, d, *J*=2Hz), 5.93 (1H, d, *J*=2Hz), 3.95 (1H, d, *J*=10Hz), 3.81 (3H, s), 3.72 (1H, m), 3.55 (1H, dd, *J*=10&5Hz), 3.46 (1H, d *J*=18Hz), 3.13 (2H, m), 3.00 (1H, d, *J*=18Hz), 2.10 (6H, s). MS (DCI, NH_3) m/e 502 (MH^+). Anal. calcd. for $C_{29}H_{30}N_2O_6 \cdot 0.5\ H_2O$: C ,68.09, H, 6.11, N, 5.48. Found: C, 67.98, H, 6.02, N, 5.33.

Example 12

trans,trans-2-(4-propoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, $CDCl_3$) δ 8.30 (1H, bs), 7.36 (2H, d, *J*=9Hz), 7.21 (1H, m), 7.09 (2H, d, *J*=10Hz), 6.91 (2H, d, *J*=9Hz), 6.59 (1H, d, *J*=2Hz), 6.51 (1H, d, *J*=2Hz), 5.93 (1H, d, *J*=2Hz), 5.91 (1H, d, *J*=2Hz), 3.93 (3H, m), 3.80 (3H, s), 3.72 (1H, m), 3.60-3.50 (2H, m), 3.15 (2H, m), 3.02 (1H, d *J*=18Hz), 2.43 (4H, q, *J*=9Hz), 1.82 (2H, m), 1.08 (6H, t, *J*=9Hz), 1.05 (3H, t, *J*=9Hz). MS (DCI, NH_3) m/e 589 (MH^+). Anal. calcd. for $C_{34}H_{40}N_2O_7 \cdot 0.25\ H_2O$: C, 68.84, H, 6.88, N, 4.72. Found: C, 68.80, H, 6.59, N, 4.52.

Example 13

trans,trans-2-(3-methoxy-4-propoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, $CDCl_3$) δ 8.22 (1H, s), 7.21 (1H, m), 7.09 (2H, d, *J*=10Hz), 7.02 (1H, dd, *J*=9&3Hz), 6.93 (1H, d, *J*=2Hz), 6.87 (1H, d, *J*=9Hz), 6.61 (1H, d, *J*=2Hz),

6.53 (1H, d, *J*=2Hz), 5.93 (1H, d, *J*=2Hz), 5.91 (1H, d, *J*=2Hz), 3.97 (3H, q, *J*=9Hz), 3.84 (3H, s), 3.82 (3H, s), 3.70 (1H, m), 3.60-3.45 (2H, m), 3.15 (2H, m), 3.02 (1H, d *J*=18Hz), 2.42 (4H, q, *J*=9Hz), 1.85 (2H, m), 1.08 (6H, t, *J*=9Hz), 1.05 (3H, t, *J*=9Hz). MS (DCI, NH_3) m/e 619 (MH^+). Anal. calcd. for $C_{35}H_{42}N_2O_8$: C, 67.94, H, 6.84, N, 4.53. Found: C, 67.65, H, 6.98, N, 4.44.

Example 14

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-dibromo)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, $CDCl_3$) δ 8.58 (1H, bs), 7.58 (2H, d, *J*=9Hz), 7.40 (2H, bd, *J*=10Hz), 7.02 (1H, t, *J*=9Hz), 6.91 (2H, d, *J*=9Hz), 6.86 (1H, m), 6.76 (1H, d, *J*=9Hz), 5.93 (2H, s), 3.98 (1H, bd, *J*=10Hz), 3.81 (3H, s), 3.73 (2H, m), 3.55 (1H, bd, *J*=15Hz), 3.13 (2H, m), 3.01 (1H, bd, *J*=18Hz). MS (DCI, NH_3) m/e 633 (MH^+). Anal. calcd. for $C_{27}H_{24}Br_2N_2O_6 \cdot 0.3\ H_2O$: C, 50.85, H, 3.89, N, 4.39. Found: C, 50.45, H, 3.48, N, 4.22.

Example 15

[*2R,3R,4S*]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, hydrochloride salt

Example 15A-E

Alternative preparation of Ethyl *trans-trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

Example 15A

5-(2-Nitrovinyl)-1,3-benzodioxole

To piperonal (15.55 kg, 103.5 mol) under mechanical stirring and under nitrogen was added ammonium acetate (13.4 kg, 173.8 mol), acetic acid (45.2 kg), and nitromethane (18.4 kg, 301.4 mol) sequentially. The mixture was warmed to 70 °C. After about 30 minutes, the yellow product began to crystallize. The reaction temperature was raised to 80 °C and stirred for about 10 hours until minimal piperonal remains. The somewhat thick reaction mixture was cooled to 10 °C and filtered. The precipitate was washed with acetic acid (2 x 8 kg) and then water (2 x 90 kg). The product was dried under a nitrogen purge and then in a vacuum oven at 50 °C for 2 days to afford 15.94 kg (80%) of the title compound as a bright yellow solid.

Example 15B

Ethyl (4-methoxybenzoyl)acetate

To potassium t-amylate (25 wt %, 50.8 kg, 99.26 mol) in toluene (15.2 kg) cooled to 5 °C under mechanical stirring and under nitrogen was added a mixture of 4-methoxyacetophenone (6.755 kg, 44.98 mol) and diethyl carbonate (6.40 kg, 54.18 mol) in toluene over 1 hour maintaining the temperature below 10 °C. The reaction mixture was heated to 60 °C for 8 hours until no 4-methoxyacetophenone was detected by HPLC. The mixture was cooled to 20 °C and quenched by adding to a mixture of acetic acid (8 kg) and water (90 kg) over 30 minutes while maintaining the temperature at <20 °C. The layers were separated, and the organic layer was washed with 5% sodium bicarbonate solution (41 kg) and concentrated to 14.65 kg. The temperature is maintained below 50 °C during the distillation. The yellow product concentrate was assayed by HPLC against an external standard and the yield was found to be 9.40 kg (94%).

Example 15C

Ethyl 2-(4-methoxybenzoyl)-4-nitromethyl-3-(1,3-benzodioxole-5-yl)butyrate

To the compound resulting from Example 15A (7.5 kg, 37.9 mol) suspended in THF (56 kg) with mechanical stirring under nitrogen was added the compound resulting from Example 15B (8.4 kg, 37.9 mol). The mixture was cooled to 17 °C, sodium ethoxide (6.4 g, 0.095 mol) was added, and the reaction was stirred for 30 minutes. After about 15 minutes, the nitrostyrene was completely dissolved. Sodium ethoxide (6.4 g, 0.095 mol) was added, and the mixture was stirred at 25 °C until HPLC shows less than 1 area % ketoester remaining. The reaction was concentrated to 32.2 kg which was determined by HPLC assay to be ~14.9 kg (95%).

Example 15D

Ethyl *cis,cis*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

Raney nickel (20.0 g), from which the water had been decanted, was charged to a stirred hydrogenator equipped with a thermocouple. THF (20 mL), the crude compound resulting from Example 15C (40.82 g, 0.0482 mol), and acetic acid (2.75 mL, 0.0482 mol) were added sequentially. The mixture was put under a hydrogen atmosphere at 60 psi until the hydrogen uptake slowed dramatically. TFA was added, and the mixture was hydrogenated at 200 psi until HPLC shows no residual imine and <2 area % nitrone. The catalyst was filtered away and washed with 100 mL of methanol. The filtrate was assayed by HPLC and found to contain 13.3 g (75%

yield) of the cis, cis-pyrrolidine compound. The filtrate was concentrated and chased with additional THF (200 mL) to give a final volume of 100 mL. The mixture was neutralized with 2 N NaOH solution (50 mL), diluted with water (200 mL), and extracted with ethyl acetate (2 x 100 mL). The combined nearly colorless ethyl acetate layers were assayed against an external standard by HPLC to be13.0 g (73%) of the title compound.

Example 15E

Ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The solution of the compound resulting from Example 15D (38.1 g, 0.103 mol) was chased with ethanol (200 mL) to a final volume of 100 mL and sodium ethoxide (3.40 g, 0.050 mol) was added. The mixture was heated to 75 °C. When HPLC shows <3% of the cis,cis isomer remaining, the mixture was cooled to room temperature. The product was assayed by HPLC against an external standard and found to contain 34.4 g (90% yield) of the title compound. The crude compound solution was concentrated and the residue taken up in isopropyl acetate (400 mL). The organic layer was washed with water (2 x 150 mL) and then extracted with 0.25 M phosphoric acid solution (2 x 400 mL). The combined phosphate layers were stirred with ethyl acetate (200 mL) and neutralized to pH 7 with solid sodium bicarbonate (21 g). The organic layer was separated and found to contain 32.9 g (87%) of the title compound.

Example 15F

Ethyl [*2R,3R,4S*]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The racemic amino ester from Example 1 (32.9 g) was dissolved in 50 mL of acetonitrile. (*S*)-(+)-Mandelic acid (2.06 g, 0.0136 mmol) was added and allowed to dissolve. The mixture was seeded with the product and allowed to stir at room temperature for 16 hours. The reaction mixture was cooled to 0 °C and stirred for 5 hours. The product was filtered and dried in a vacuum oven with a nitrogen purge for 1 day at 50 °C. The resultant salt (20.0 g, 0.0383 mol) was suspended in ethyl acetate (150 mL) and 5% sodium bicarbonate solution (150 mL). The mixture was stirred at room temperature until the salt dissolved and carbon dioxide evolution had ceased. The organic layer was separated and concentrated.

Example 15G

[2R,3R,4S]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared from the compound of Example 15F according to the procedures of Example 1E.

Example 15H

[2R,3R,4S]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, hydrochloride salt

The compound of Example 15G (450 mg) was dissolved in 10 mL of isopropanol. A slight excess of saturated HCl in ethanol was added, and the resultant solution was stirred for 10 min. The solvents were removed *in vacuo*, and the excess HCl was chased with isopropanol. The residue was taken up in ether and filtered, leaving 448 mg of the title compound as a white solid. MS (DCI/NH_3) m/e 531 $(M+H)^+$. Anal calcd for $C_{31}H_{35}N_2O_6Cl$: C, 65.66 H, 6.22; N, 4.94. Found: C, 65.72; H, 6.39; N, 4.65.

Example 16

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-dimethoxy)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 16A

2,6-Dimethoxyaniline

To a stirred solution of 2,6-dimethoxybenzoic acid (2.00 g, 11.0 mmol) in 1,2-dichloroethane (45 mL) at ambient temperature was successively added N-methylmorpholine (1.45 mL, 13.2 mmol) and diphenylphosphoryl azide (2.60 mL, 12.1 mmol). After heating the mixture for 2 hours at 75 °C, cuprous iodide (150 mg) and benzyl alcohol (2.27 mL, 22.0 mmol) were added and heating was continued overnight. Solvents were removed *in vacuo* and the residue was chromatographed on silica gel, eluting with 4:1 hexane-ethyl acetate to give the intermediate carbamate (1.50 g, 48 % yield) as a white, crystalline solid. The solid was dissolved in methanol (15 mL) and added to a flask purged with nitrogen containing 10% palladium-on-charcoal (500 mg). The mixture was placed under a balloon of hydrogen and stirred

4 hours at ambient temperature. The mixture was filtered through a pad of Celite and solvents were removed *in vacuo* to give the title compound (800 mg, 48% yield).

Example 16B

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-dimethoxy)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1, substituting the compound of Example 16A for 2,4,6-trimethylaniline in Example 1D. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.18 (1H, bs), 7.39 (2H, bd, *J*=9Hz), 7.17 (1H, t, *J*=9Hz), 6.99 (1H, d, *J*=2Hz), 6.90 (2H, d, *J*=9Hz), 6.86 (1H, d, *J*=2Hz), 6.75 (1H, d, *J*=9Hz), 6.56 (2H, d, *J*=9Hz), 5.93 (2H, s), 3.88 (1H, bd, *J*=10Hz), 3.81 (3H, s), 3.71 (6H, s), 3.70 (2H, m), 3.49 (1H, bd, *J*=15Hz), 3.03 (2H, m), 2.85 (1H, bd, *J*=18Hz). NMR (DCI, NH_3) m/e 535 (MH^+). Anal. calcd. for $C_{29}H_{30}N_2O_8 \cdot 0.75$ AcOH: C, 63.20, H, 5.74, N, 4.83. Found: C, 63.18, H, 5.34, N, 4.79.

Example 17

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((4-bromo-2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 17A

4-Bromo-2,6-diethylaniline

To a stirred solution of 2,6-diethylaniline (10.0 g, 67.0 mmol) in acetic acid (50 mL) at ambient temperature was added bromine (10.4 mL, 201 mmol). The reaction was stirred overnight at ambient temperature. The reaction mixture was diluted with diethyl ether (200 mL) and washed with 5% sodium bisulfite (4 x 50 mL) and brine. The organic phase was dried with sodium sulfate and the solvents were removed *in vacuo*. The residue was chromatographed on silica gel, eluting with 9:1 hexane-ethyl acetate to give the title compound (3.28 g, 21% yield).

Example 17B

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((4-bromo-2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1, substituting the compound of Example 17A for 2,4,6-trimethylaniline in Example 1D. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.21 (1H, bs), 7.38 (2H, d, *J*=9Hz), 7.23 (2H, s), 6.92 (2H, d, *J*=9Hz), 6.88 (1H, d, *J*=2Hz), 6.82 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=9Hz), 5.93 (1H, d, *J*=2Hz), 5.91 (1H, d, *J*=2Hz), 3.95 (1H, d, *J*=9Hz), 3.82 (3H, s), 3.72 (1H, m), 3.52 (1H, m), 3.45 (1H, d *J*=18Hz), 3.14 (2H, m), 3.00 (1H, d, *J*=18Hz), 2.39 (4H, q, *J*=9Hz), 1.07 (6H, t, *J*=9Hz). MS (DCI, NH_3) m/e 609 (MH^+). Anal. calcd. for $C_{31}H_{33}BrN_2O_6$: C, 61.09, H, 5.46, N, 4.60. Found: C, 60.80, H, 5.35, N, 4.54.

Example 18

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2-ethyl-6-methyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.32 (1H, bs), 7.38 (2H, d, *J*=9Hz), 7.20-7.10 (3H, m), 6.92 (2H, d, *J*=9Hz), 6.87 (1H, d, *J*=2Hz), 6.82 (1H, dd, *J*=8&2Hz), 6.76 (1H, d, *J*=9Hz), 5.94 (1H, d, *J*=2Hz), 5.92 (1H, d, *J*=2Hz), 3.95 (1H, d, *J*=9Hz), 3.82 (3H, s), 3.73 (1H, m), 3.55 (1H, dd, J=12&6), 3.47 (1H, d *J*=18Hz), 3.14 (2H, m), 3.02 (1H, d, *J*=18Hz), 2.44 (2H, q, *J*=9Hz), 2.10 (3H, s), 1.10 (3H, t, *J*=9Hz). MS (DCI, NH_3) m/e 517 (MH^+). Anal. calcd. for $C_{30}H_{32}N_2O_6 \cdot 0.5\ H_2O$: C, 68.56, H, 6.33, N, 5.33. Found: C, 68.58, H, 6.29, N, 5.13.

Example 19

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-triethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 19A

Ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-triethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylate

To a mixture (purged with nitrogen) of [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (1:1 complex with dichloromethane) (13 mg) and cesium carbonate (307 mg, 0.942 mmol) in anhydrous N,N-dimethylformamide (2 mL) at

ambient temperature was added ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-bromo-2,6-diethylphenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylate (200 mg, 0.314 mmol, prepared in Example 17) in anhydrous tetrahydrofuran (8 mL). After stirring the mixture for 10 minutes at ambient temperature, 1.0 M triethylborane (0.471 mL, 0.471 mmol) in tetrahydrofuran was added. The reaction was stirred overnight at 65 °C under nitrogen. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (2 x 30 mL) and brine. The organic phase dried with sodium sulfate, and the solvents were removed *in vacuo* . The residue was chromatographed on silica gel eluting with 3:1 hexane-ethyl acetate to give the title compound (110 mg, 60 % yield).

Example 19B

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,4,6-triethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1E. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.22 (1H, bs), 7.38 (2H, d, *J*=9Hz), 6.95 (2H, s), 6.91 (2H, d, *J*=9Hz), 6.84 (1H, d, *J*=2Hz), 6.82 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=9Hz), 5.93 (1H, d, *J*=2Hz), 5.91 (1H, d, *J*=2Hz), 3.95 (1H, d, *J*=10Hz), 3.82 (3H, s), 3.71 (1H, m), 3.52 (1H, dd, *J*=9&2Hz), 3.46 (1H, d *J*=18Hz), 3.13 (2H, m), 3.00 (1H, d, *J*=18Hz), 2.60 (2H, q, *J*=9Hz), 2.40 (4H, q, *J*=9Hz), 1.22 (3H, t, *J*=9Hz), 1.08 (6H, t, *J*=9Hz). MS (DCI, NH_3) m/e 559 (MH^+). Anal. calcd. for $C_{33}H_{38}N_2O_6 \cdot 0.25\ H_2O$: C, 70.38, H, 6.89, N, 4.97. Found: C, 70.18, H, 7.14, N, 4.63.

Example 20

[*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 20A

[*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-*tert*-butoxycarbonyl-pyrrolidine-3-carboxylic acid

The racemic amino ester from Example 3 (8.00 g) was combined with 4.45 g of di-tert-butyldicarbonate in 100 mL of THF; 10 mL of triethylamine was added, and the resultant solution was stirred at ambient temperature for 3 hrs. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with aqueous 1N H_3PO_4, bicarb, and brine. The crude product was dissolved in 30 mL of

ethanol; 12 mL of 2.5 N NaOH solution was added, the mixture was stirred overnight at ambient temperature, then warmed to 50 °C for 2 hrs. The solvents were removed *in vacuo*; the residue was partitioned between water and ether. The aqueous extract was acidified with aqueous 1N H_3PO_4 and extracted twice with EtOAc. The organic extracts were washed with brine and dried over Na_2SO_4 to give 9.2 g of *trans,trans*-2-(4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-tert-butoxycarbonyl-pyrrolidine-3-carboxylic acid. This material was dissolved in 30 mL of EtOAc, and 1.3 mL of (R)-(+)-α-methylbenzylamine was added. The solution was stirred for 10 min; the solvents were removed *in vacuo*, 50 mL of ether were added, and the resultant solution was seeded. After standing overnight, the solvents were removed in vacuo; the residue was taken up in 70 mL of ether and filtered. The solid product was recrystallized from EtOAc / ether. The crystalline material was stirred vigorously in a two-phase mixture of 1N H_3PO_4 and EtOAc; the organic layer was decanted, then washed with brine and dried over Na_2SO_4.

Example 20B

Ethyl [*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The compound of Example 20A was dissolved in ethanol and cooled in an ice bath. Gaseous HCl was bubbled through the solution until saturated; the resultant solution was warmed to ambient temperature and allowed to stir overnight under a blanket of nitrogen. The solvents were removed *in vacuo*; the residue was taken up in bicarb and extracted with EtOAc. The organic layer was decanted, then washed with brine and dried over Na_2SO_4.

Example 20C

[*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethylphenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared from the compound of Example 20B according to the procedures of Example 1E. MS (DCI/NH_3) m/e 559 $(M+H)^+$. Anal calcd for $C_{33}H_{38}N_2O_6 \cdot 0.2\ H_2O$: C, 70.49; H, 6.88; N, 4.98. Found: C, 70.52; H, 6.78; N, 4.85.

Example 21

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diisopropyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^{1}H NMR (300MHz, $CDCl_3$, δ) 8.29 (1H, bs), 7.39 (2H, d, *J*=9Hz), 7.29 (1H, m), 7.15 (2H, d, *J*=9Hz), 6.93 (2H, d, *J*=9Hz), 6.85 (1H, d, *J*=2Hz), 6.83 (1H, dd, *J*=8&2Hz), 6.74 (1H, d, *J*=9Hz), 5.93 (1H, d, *J*=2Hz), 5.91 (1H, d, *J*=2Hz), 3.96 (1H, d, *J*=10Hz), 3.83 (3H, s), 3.73 (1H, m), 3.55 (1H, dd, J=12&6), 3.50 (1H, d *J*=18Hz), 3.14 (2H, m), 3.01 (1H, d, *J*=18Hz), 2.84 (2H, m), 1.16 (6H, d, *J*=8Hz), 1.05 (6H, d *J*=8Hz). MS (DCI, NH_3) m/e 559 (MH^+). Anal. calcd. for $C_{33}H_{38}N_2O_6 \cdot 0.5\ H_2O$: C, 69.82, H, 6.92, N, 4.93. Found: C, 69.69, H, 6.63, N, 4.89.

Example 22

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl-4-methyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 19. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.20 (1H, bs), 7.38 (2H, d, *J*=9Hz), 6.92 (4H, m), 6.86 (1H, d, *J*=2Hz), 6.82 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=9Hz), 5.93 (1H, d, *J*=2Hz), 5.91 (1H, d, *J*=2Hz), 3.95 (1H, d, *J*=10Hz), 3.81 (3H, s), 3.72 (1H, m), 3.55 (1H, dd, *J*=9&2Hz), 3.45 (1H, d *J*=18Hz), 3.13 (2H, m), 3.00 (1H, d, *J*=18Hz), 2.39 (4H, q, *J*=9Hz), 2.28 (3H, s), 1.07 (6H, t, *J*=9Hz). NMR (DCI, NH_3) 545 m/e (MH^+). Anal. calcd. for $C_{32}H_{36}N_2O_6 \cdot 0.5\ H_2O$: C, 69.42, H, 6.74, N, 5.06. Found: C, 69.43, H, 6.57, N, 4.94.

Example 23

(2*R*,3*R*,4*S*)-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared from the racemic amino ester of Example 10 according to the procedures of Example 20. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.32 (1H, bs), 7.38 (2H, d, *J*=9Hz), 7.21 (1H, m), 7.12 (2H, d, *J*=10Hz), 6.90 (3H, m), 6.83 (1H, dd, *J*=8&2Hz), 6.74 (1H, d, *J*=9Hz), 5.94 (1H, d, *J*=2Hz), 5.92 (1H, d, *J*=2Hz), 4.05 (2H, m), 3.96 (1H, d, *J*=10Hz), 3.72 (1H, m), 3.53 (1H, dd, *J*=10&3Hz), 3.47 (1H, d, *J*=18Hz), 3.13 (2H, m), 3.02 (1H, d *J*=18Hz), 2.44 (4H, q, *J*=9Hz), 1.42 (3H, t, *J*=9Hz),

1.08 (6H, t, *J*=9Hz). MS (DCI, NH_3) m/e 545 (MH^+). Anal. calcd. for $C_{32}H_{36}N_2O_6 \cdot 0.5$ H_2O: C, 69.42, H, 6.74, N, 5.06. Found: C, 69.67, H, 6.73, N, 4.98.

Example 24

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((4-carboxy-2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 19. ^1H NMR (300MHz, DMSO) δ 7.68 (2H, bs), 7.54 (2H, d, *J*=9Hz), 7.27 (2H, m), 6.93 (2H, d, *J*=9Hz), 6.83 (2H, m), 5.98 (2H, s), 3.92 (1H, d, *J*=9Hz), 3.76 (3H, s), 3.62 (1H, m), 3.45-3.00 (2H, m), 3.00-2.80 (3H, m), 2.44 (4H, q, *J*=9Hz), 1.04 (6H, t, *J*=9Hz). NMR (DCI, NH_3) m/e 575 (MH^+). Anal. calcd. for $C_{32}H_{34}N_2O_8 \cdot 0.5$ H_2O: C, 65.85, H, 6.04, N, 4.80. Found: C, 66.03, H, 5.84, N, 4.67.

Example 25

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((4-nitro-2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 25A

2,6-Diethyl-4-nitroaniline

To a stirred solution of 2,6-diethylaniline (5.0 g, 34 mmol) in concentrated sulfuric acid (30 mL) at 0 °C was added dropwise concentrated nitric acid (15.9 M, 2.10 mL, 34 mmol). The cooling bath was removed, and the reaction was stirred for 3 hours at ambient temperature. After pouring the reaction mixture into ice, the solution was neutralized using 4 N sodium hydroxide and extracted with methylene chloride (3 x 50 mL). The extracts were dried with sodium sulfate, and solvents were removed *in vacuo* to give the title compound.

Example 25B

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((4-nitro-2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1, substituting the compound of Example 25A for 2,4,6-trimethylaniline in Example 1D. ^1H NMR (300MHz, $CDCl_3$) δ 8.38 (1H, bs), 7.77 (1H, d, *J*=9Hz), 7.38 (2H, d, *J*=9Hz),

7.24 (1H, d, *J*=9Hz), 6.92 (2H, d, *J*=9Hz), 6.88 (1H, d, *J*=2Hz), 6.82 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=9Hz), 5.93 (1H, d, *J*=2Hz), 5.91 (1H, d, *J*=2Hz), 3.97 (1H, d, *J*=9Hz), 3.83 (3H, s), 3.74 (1H, m), 3.48 (2H, m), 3.18 (2H, m), 3.04 (1H, d, *J*=18Hz), 2.63 (2H, m), 2.44 (2H, q, *J*=9Hz), 1.10 (3H, t, *J*=9Hz), 1.08 (3H, t, *J*=9Hz). MS (DCI, NH_3) m/e 576 (MH^+). Anal. calcd. for $C_{31}H_{33}N_3O_8 \cdot 0.75\ H_2O$: C, 63.20, H, 5.90, N, 7.13. Found: C, 63.30, H, 5.81, N, 7.14.

Example 26

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2-isopropyl-6-methyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, $CDCl_3$) δ 8.35 (1H, bs), 7.39 (2H, d, *J*=9Hz), 7.18 (2H, m), 7.07 (1H, dd, *J*=9&2Hz), 6.92 (2H, d, *J*=9Hz), 6.86 (1H, d, *J*=2Hz), 6.82 (1H, dd, *J*=8&2Hz), 6.75 (1H, d, *J*=9Hz), 5.94 (1H, d, *J*=2Hz), 5.92 (1H, d, *J*=2Hz), 3.96 (1H, d, *J*=10Hz), 3.83 (3H, s), 3.72 (1H, m), 3.50 (2H, m), 3.15 (2H, m), 3.02 (1H, d, *J*=18Hz), 2.86 (1H, m), 2.09 (3H, s), 1.16 (3H, d, *J*=8Hz), 1.07 (3H, d *J*=8Hz). MS (DCI, NH_3) m/e 531 (MH^+). Anal. calcd. for $C_{31}H_{34}N_2O_6 \cdot 0.5\ H_2O$: C, 69.00, H, 6.54, N, 5.19. Found: C, 69.27, H, 6.67, N, 5.21.

Example 27

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2-ethyl-6-methoxy)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 27A

Ethyl 3-oxo-4-(3-methoxy-2-nitrophenyl)propionate

Potassium ethylmalonate (3.68 g) was combined with 2.29 g of magnesium chloride in 12 mL of DMF; the reaction mixture was heated at 60 °C for 4 hrs. The resultant mixture was cooled to ambient temperature. Simultaneously, 3-methoxy-2-nitrobenzoic acid (3.4 g) was dissolved in 12 mL of DMF; 3.06 g of 1,1-carbonyldiimidazole was added (gas evolves), and the resultant solution (after stirring at ambient temperature for 4 hrs) was added to the malonate mixture. The resultant slurry was stirred at ambient temperature for 14 hrs. Solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with 1N H_3PO_4, bicarb, and brine, and was concentrated *in vacuo*..

Example 27B

2-Nitro-3-(1-hydroxyethyl)anisole

The compound of Example 27A (3.2 g) was dissolved in 50 mL of concentrated sulfuric acid and stirred at ambient temperature for 48 hrs. The reaction mixture was poured onto 300 mL of ice and extracted twice with EtOAc. The organic extracts were washed sequentially with water, bicarb, and brine, and were concentrated *in vacuo*. The crude product was heated neat at 160 °C for 3 hrs. The resultant dark brown residue was extracted with EtOAc. The organic extracts were concentrated. The crude product was dissolved in 15 mL of ethanol; sodium borohydride (450 mg) was added, and the resultant solution was stirred at ambient temperature for for 2 hrs. The solvents were removed *in vacuo*; the residue was taken up in 10% aqueous HCl and stirred for 15 min. The mixture was extracted with EtOAc; the organic extracts were washed sequentially with bicarb and brine, and were concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 1:1 EtOAc/hexanes, to give 1.08 g (32% overall) of the title compound as a colorless oil.

Example 27C

2-Ethyl-6-methoxyaniline

The compound of Example 27B (310 mg) was dissolved in 10 mL of THF; 1.5 mL of H3PO4 was added, followed by 50 mg of 10% palladium-on-charcoal. The resultant mixture was purged with nitrogen, then placed under a balloon of hydrogen, and stirred overnight. Bicarb was added carefully, and the mixture was filtered through a pad of Celite. The filtrate was extracted with EtOAc; the organic extracts were washed with bicarb and brine, and were concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 1:1 ether/hexanes, to give 102 mg (43% yield) of the title compound as a colorless oil.

Example 27D

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2-ethyl-6-methoxy)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared according to the procedures of Example , substituting the compound of Example 27C for 2,4,6-trimethylaniline. ^{1}H NMR (300 MHz, CD_3OD) δ 1.10 (t, J=8 Hz, 3H), 2.48 (d, J=8 Hz, 2H), 3.4-3.9 (m, 7H), 3.73 (s,

3H), 3.84 (s, 3H), 5.93 (s, 2H), 6.80 (d, J=8 Hz, 1H), 6.86 (d, J=8 Hz, 2H), 6.93 (dd, J=2,8 Hz, 1H), 7.03 (bd d, J=9 Hz, 2H), 7.07 (d, J=2 Hz, 1H), 7.23 (t, J=8 Hz, 1H), 7.53 (bd d, J=9 Hz, 2H). MS (APCI) m/e 533 $(M+H)^+$. Anal calcd for $C_{30}H_{32}N_2O_7 \cdot 0.7$ TFA: C, 61.59 H, 5.38; N, 4.57. Found: C, 61.27; H, 5.44; N, 4.61.

Example 28

trans,trans-2-(4-*iso*-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, $CDCl_3$) δ 7.51 (2H, bd d, *J*=9Hz), 7.22 (1H, dd, *J*=8,9Hz), 7.13 (1H, s), 7.11 (1H, dd, *J*=1,8Hz), 7.05 (1H, d, *J*=2Hz), 6.99 (2H, bd d, *J*=9Hz), 6.91 (1H, dd, *J*=2,8Hz), 6.78 (1H, d, *J*=8Hz), 5.93 (1H, d, *J*=3Hz), 5.92 (1H, d, *J*=3Hz), 4.64 (1H, septet, *J*=7Hz), 3.80 (3H, m), 3.55 (2H, m), 2.47 (4H, q, *J*=7Hz), 1.33 (6H, dd, *J*=2,7Hz), 1.09 (6H, t, *J*=7Hz). MS (ESI+) m/e 559 $(M+H^+)$. Anal. Calc for $C_{33}H_{38}N_2O_6 \cdot 0.7$ TFA: C, 64.71, H, 6.11, N 4.39. Found: C, 64.54, H, 5.78, N, 4.21.

Example 29

trans,trans-2-(2-Fluoro-4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, $CDCl_3$) δ 1.06 (t, 3H, J=7Hz), 1.09 (t, 6H, J=7Hz), 1.83 (m, 2H), 2.44 (q, 4H, J=7Hz), 3.4-3.9 (m, 5H), 3.99 (t, 2H, J=6Hz), 5.95 (dd, 2H, J=1,2Hz), 6.8-6.9 (m, 4H), 7.03 (d, 1H, J=2Hz), 7.11 (d, 1H, J=8Hz), 7.13 (s, 1H), 7.22 (dd, 1H, J=7,9Hz), 7.63 (t, 1H, J=9Hz). MS (ESI+) m/e 577 $(M+H^+)$. Anal. Calc for $C_{33}H_{37}N_2O_6F \cdot 1.0$TFA: C, 60.87, H, 5.55, N 4.06. Found: C, 60.74, H, 5.61, N, 3.97.

Example 30

trans,trans-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, $CDCl_3$) δ 1.08 (t, J=7Hz, 6H), 2.43 (q, J=7Hz, 4H), 3.00 (d, J=11Hz, 1H), 3.05-3.15 (m, 2H), 3.44 (s, 3H), 3.46 (d, J=11Hz, 1H), 3.45-3.55 (m, 1H), 3.65-3.75 (m, 1H), 3.75-3.80 (m, 2H), 3.93 (d, J=7Hz, 1H), 4.12-4.17 (m, 2H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.75 (d, J=8Hz, 1H), 6.82 (dd, J=2Hz, 9Hz, 1H), 6.87 (d, J=2Hz, 1H), 6.95 (d, J=8Hz, 1H), 7.10 (d, J=6Hz, 2H), 7.19-7.24 (m, 1H), 7.37 (d,

d=8Hz, 2H), 8.29 (s, 1H). MS (APCI+) m/e 575 ($M+H^+$). Anal. Calc for $C_{33}H_{38}N_2O_7$: C, 68.97 H, 6.67, N 4.87. Found: C, 68.92, H, 6.83, N, 4.77.

Example 30A

Ethyl [4-(2-methoxyethoxy)benzoyl]-acetate

Methyl 4-hydroxybenzoate was reacted with 1-bromo-2-methoxyethane, and potassium carbonate in dimethylformamide. The resultant ester was hydrolyzed to the acid with NaOH in alcohol. This acid was reacted with carbonyl diimidazole in THF; the resulting imidazolide was reacted with the potassium salt of the mono ethyl ester of malonic acid, and magnesium chloride, to give the title compound as a colorless oil.

Example 30B

trans,trans-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1, employing the b-ketoester described above as starting material. ^1H NMR (300MHz, $CDCl_3$) d 1.08 (t, J=7Hz, 6H), 2.43 (q, J=7Hz, 4H), 3.00 (d, J=11Hz, 1H), 3.05-3.15 (m, 2H), 3.44 (s, 3H), 3.46 (d, J=11Hz, 1H), 3.45-3.55 (m, 1H), 3.65-3.75 (m, 1H), 3.75-3.80 (m, 2H), 3.93 (d, J=7Hz, 1H), 4.12-4.17 (m, 2H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.75 (d, J=8Hz, 1H), 6.82 (dd, J=2Hz, 9Hz, 1H), 6.87 (d, J=2Hz, 1H), 6.95 (d, J=8Hz, 1H), 7.10 (d, J=6Hz, 2H), 7.19-7.24 (m, 1H), 7.37 (d, d=8Hz, 2H), 8.29 (s, 1H). MS (APCI+) m/e 575 ($M+H^+$). Anal. Calc for $C_{33}H_{38}N_2O_7$: C, 68.97 H, 6.67, N 4.87. Found: C, 68.92, H, 6.83, N, 4.77.

The following compounds of Examples 31- 857 can be prepared using the methods described in the above examples.

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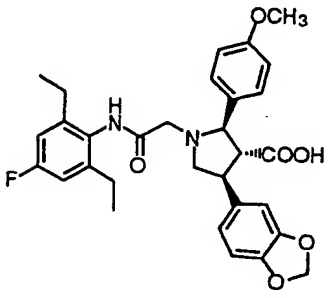

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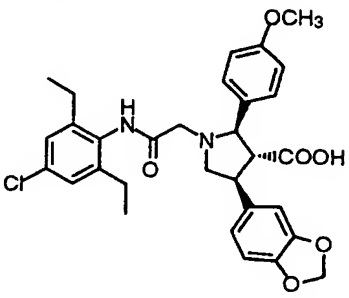

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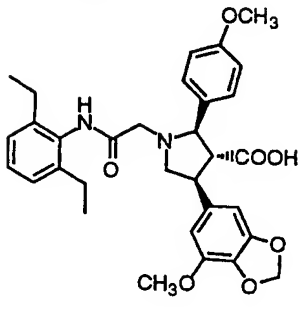

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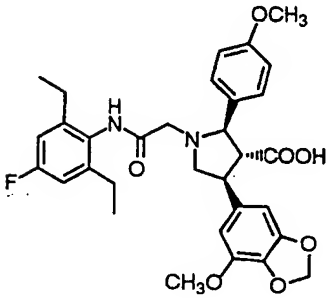

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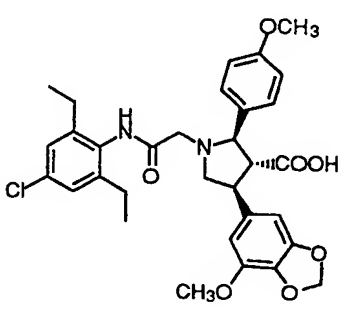

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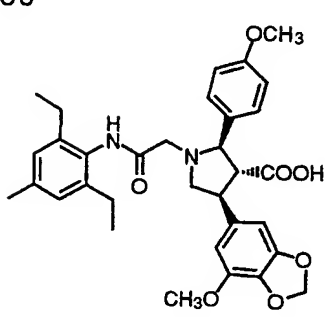

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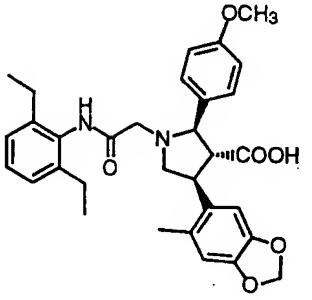

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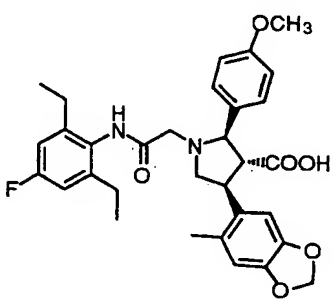

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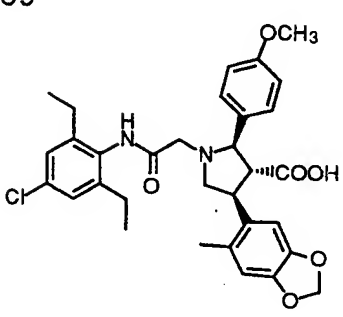

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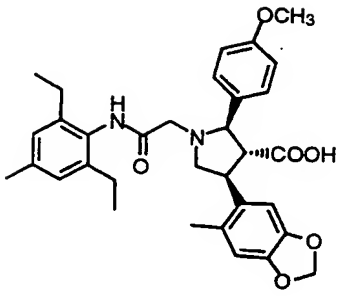

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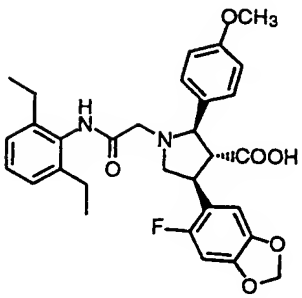

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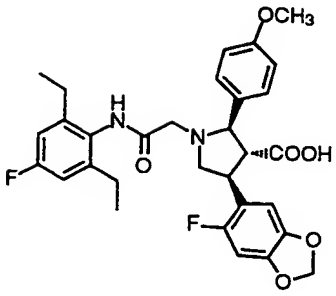

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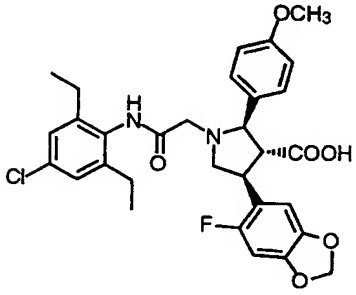

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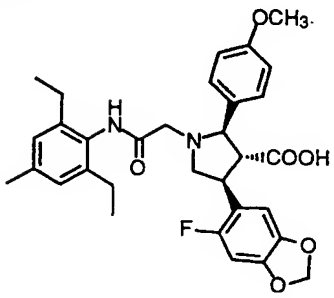

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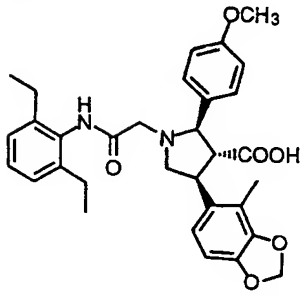

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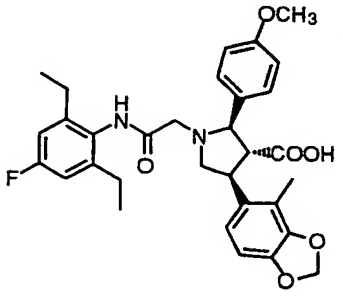

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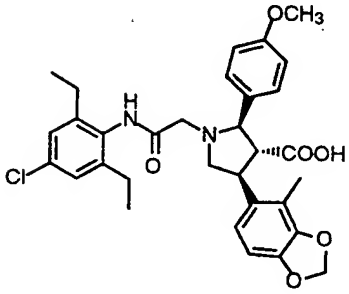

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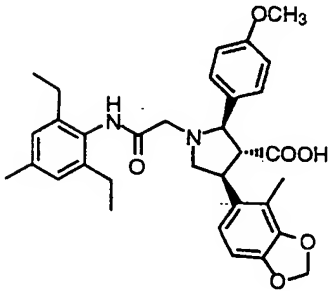

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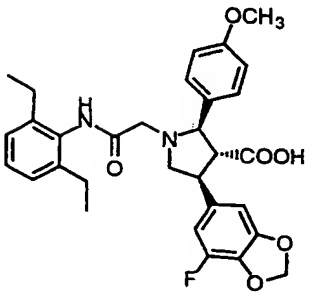

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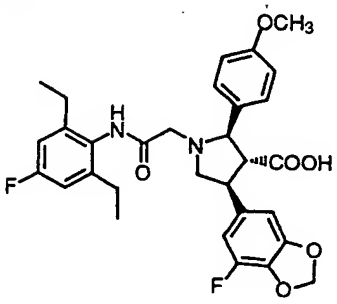

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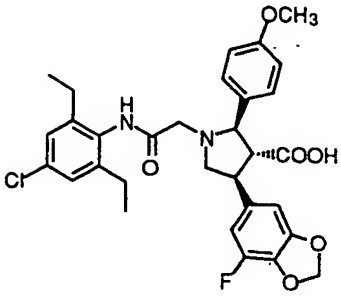

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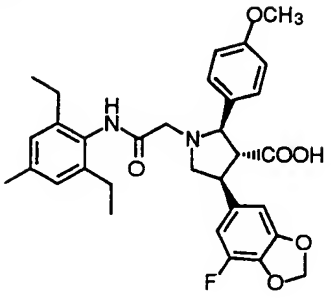

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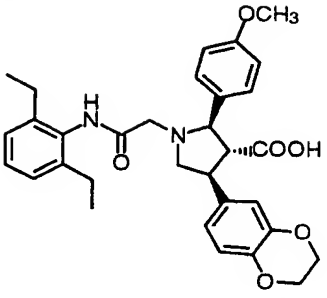

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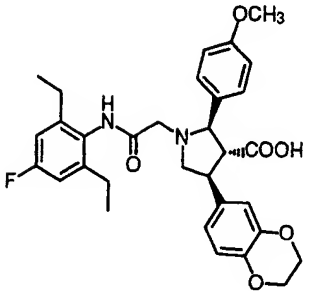

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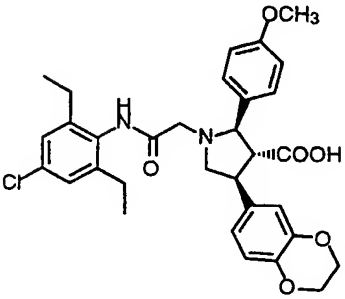

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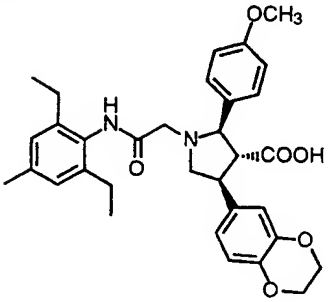

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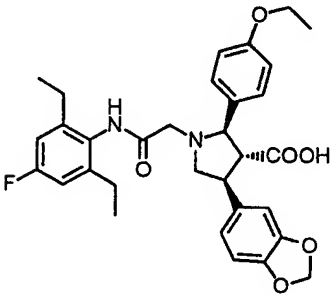

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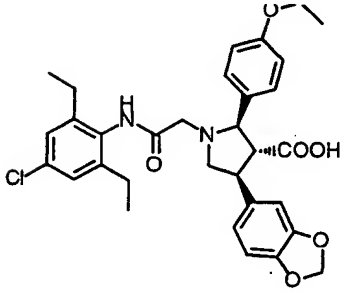

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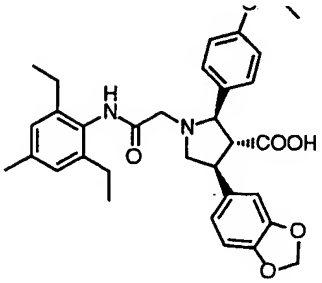

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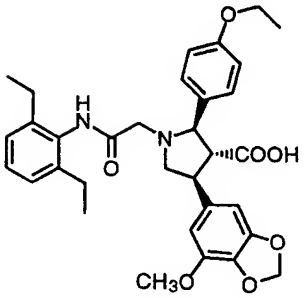

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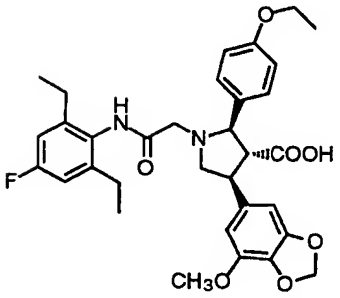

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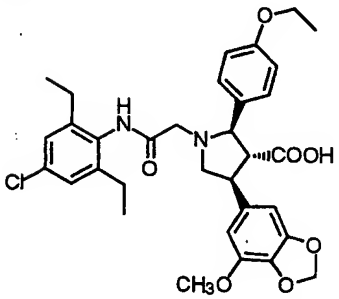

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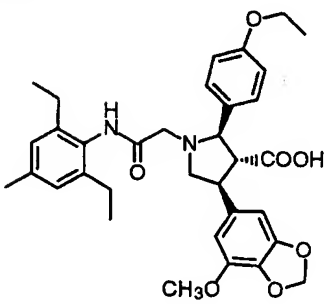

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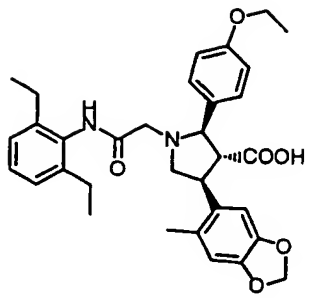

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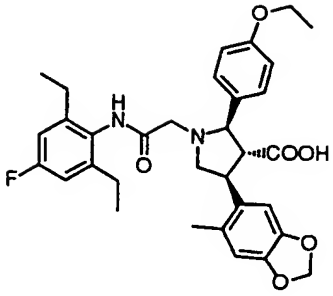

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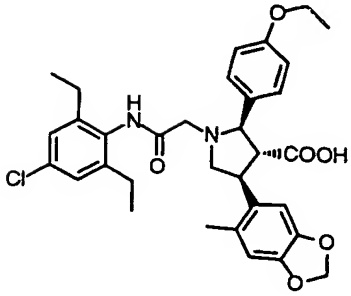

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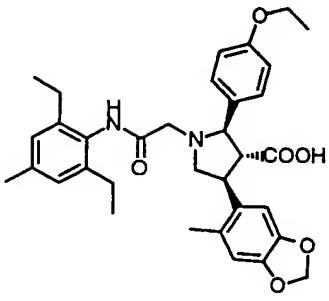

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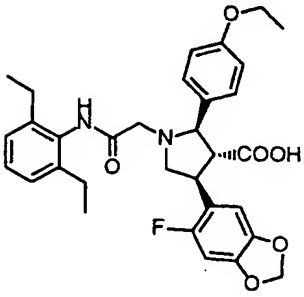

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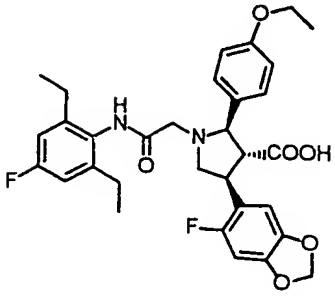

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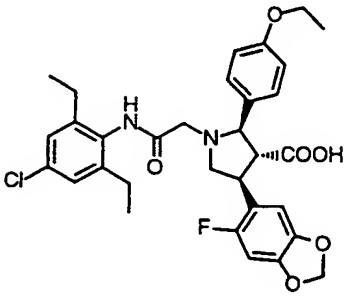

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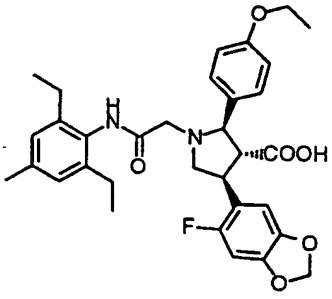

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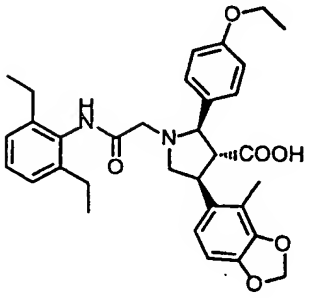

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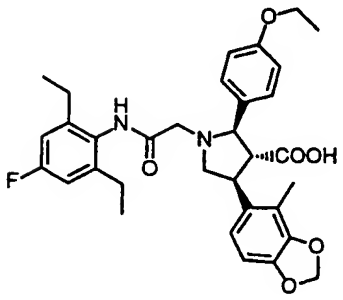

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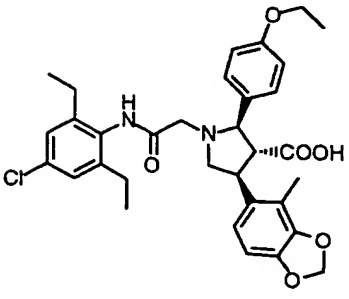

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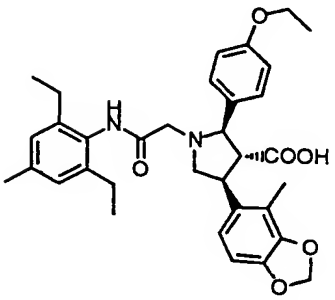

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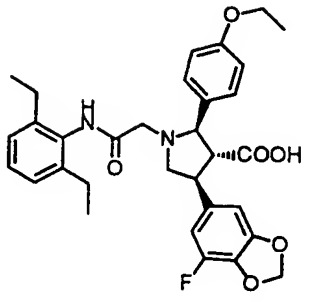

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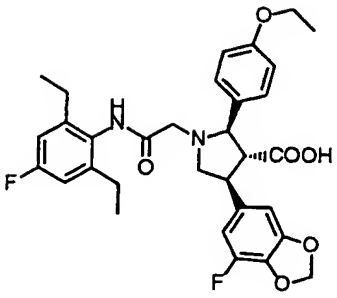

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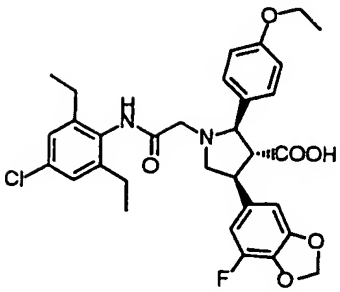

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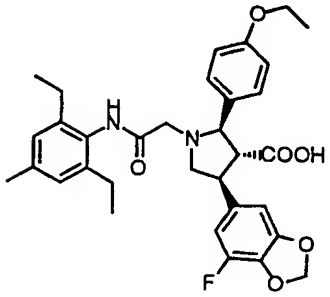

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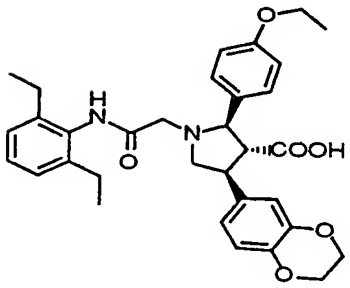

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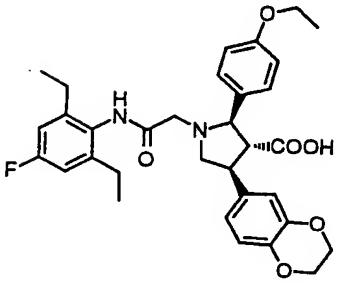

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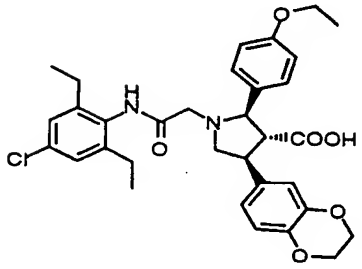

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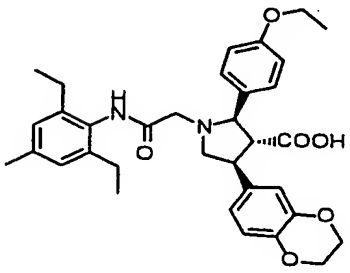

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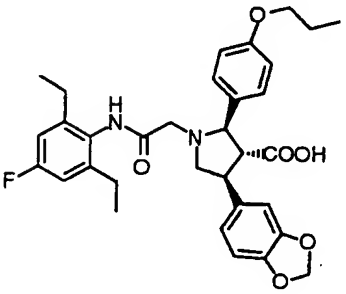

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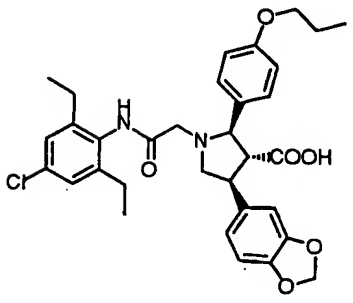

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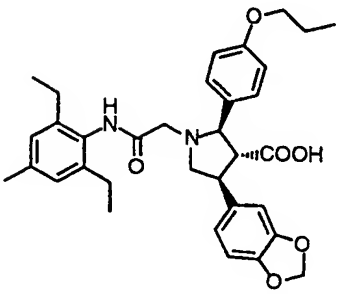

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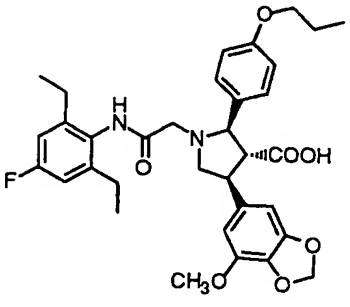

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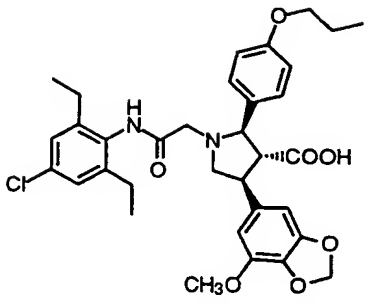

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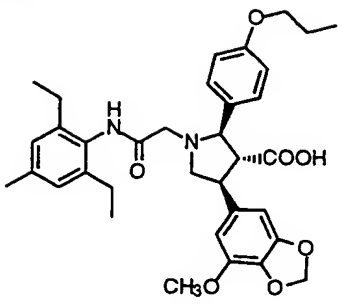

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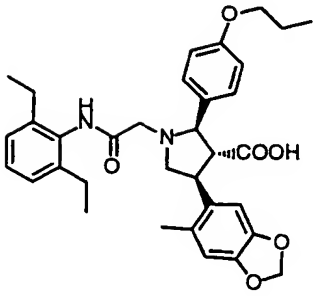

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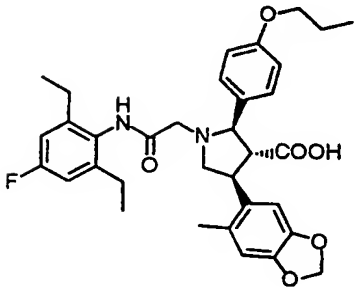

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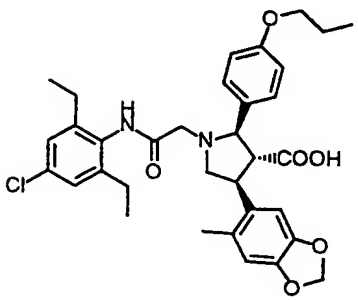

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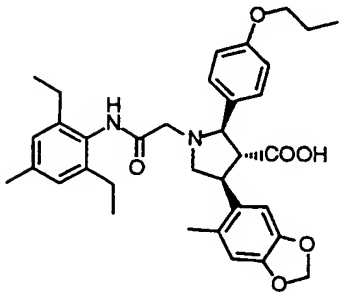

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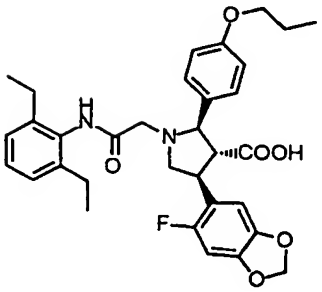

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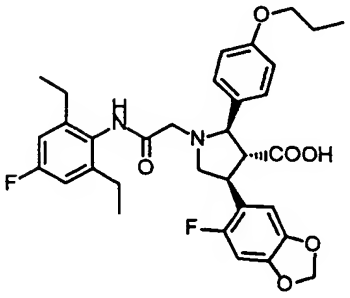

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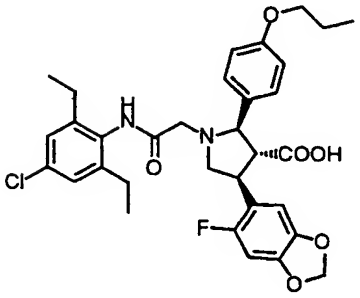

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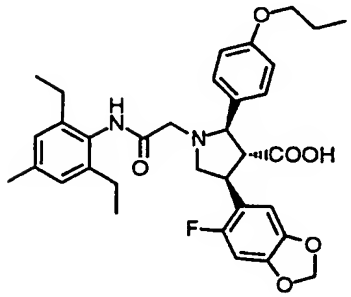

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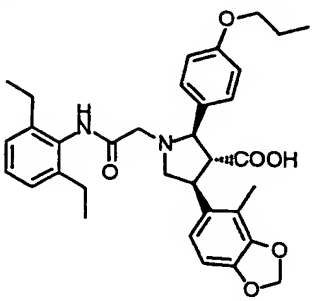

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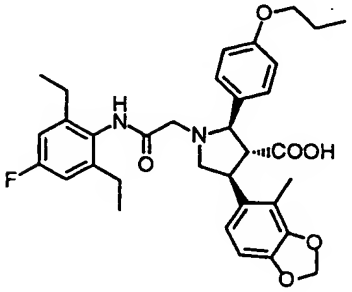

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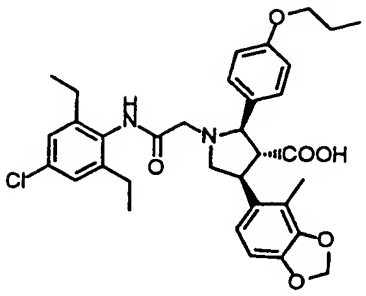

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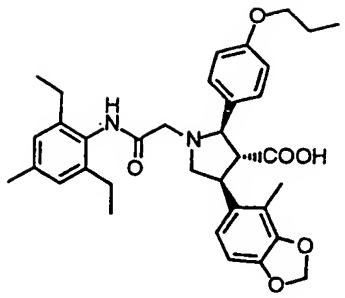

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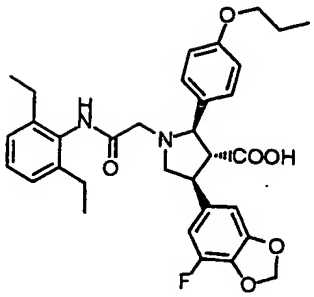

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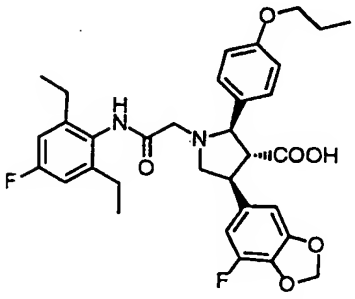

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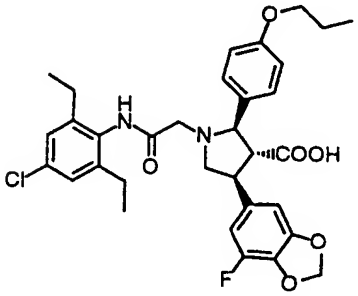

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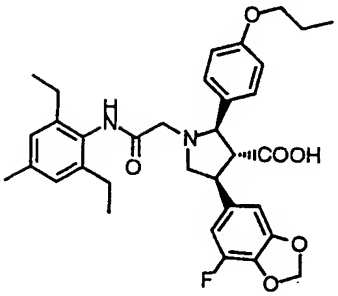

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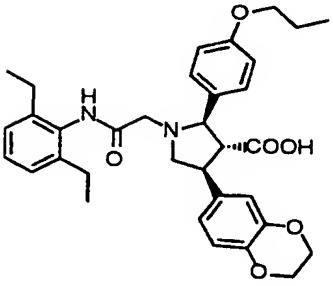

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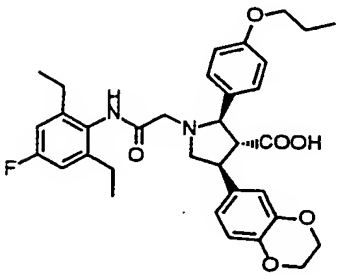

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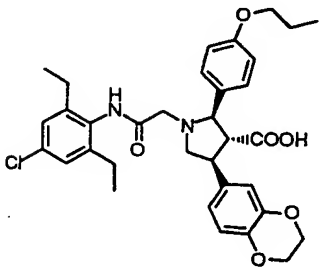

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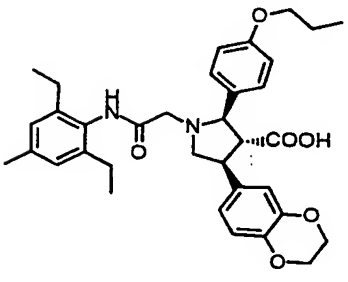

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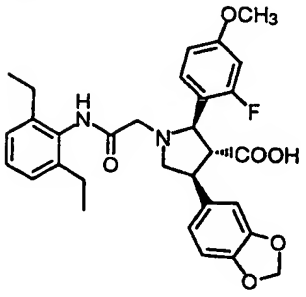

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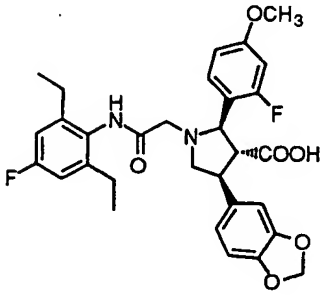

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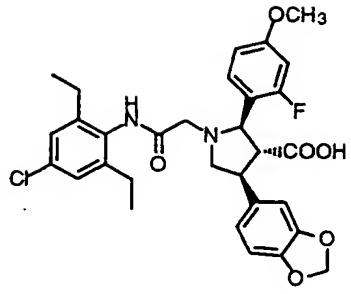

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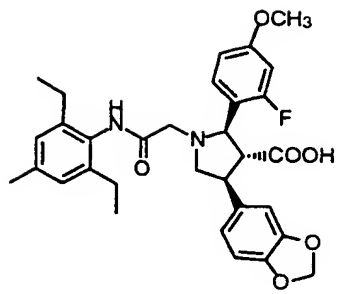

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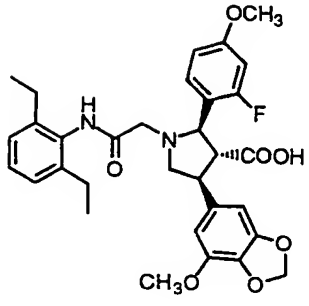

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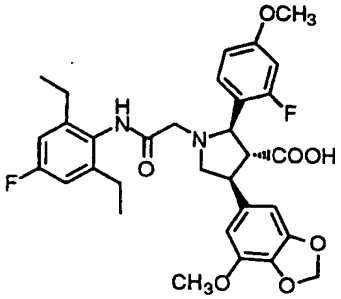

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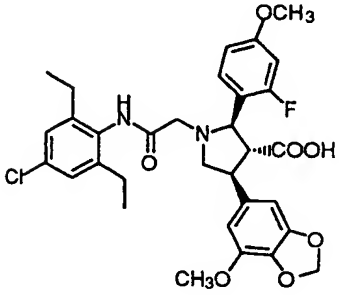

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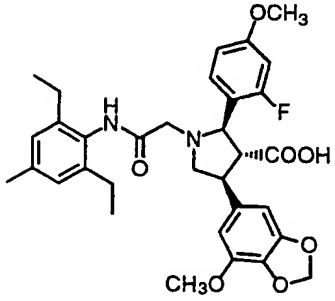

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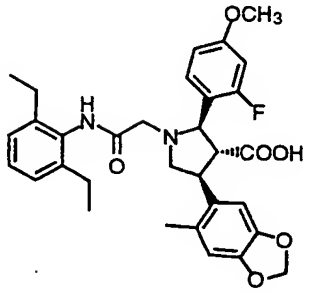

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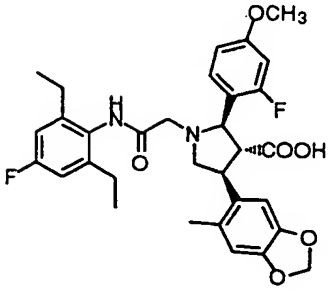

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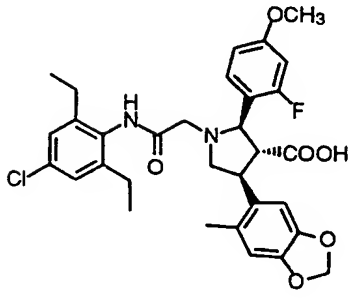

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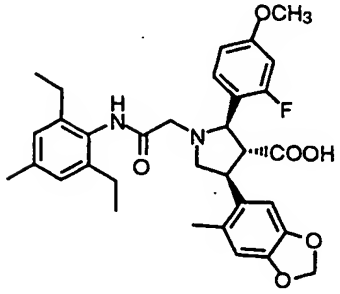

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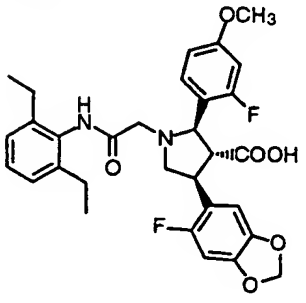

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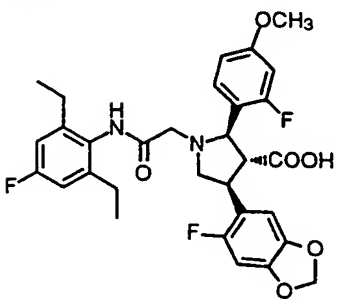

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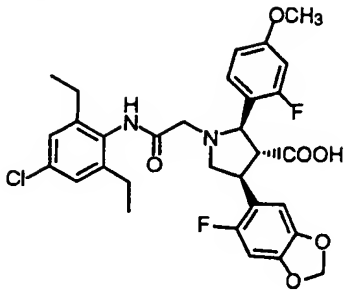

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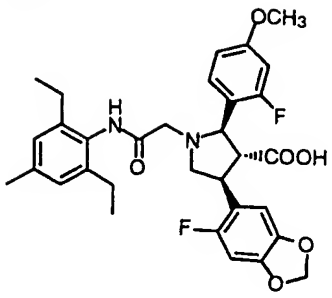

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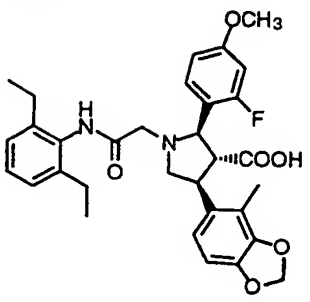

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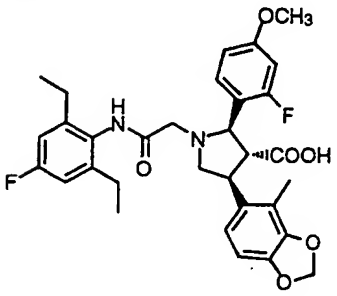

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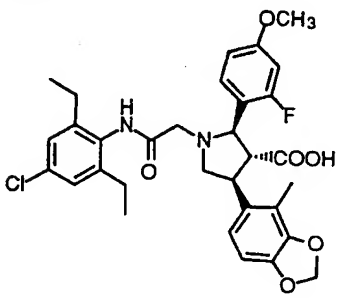

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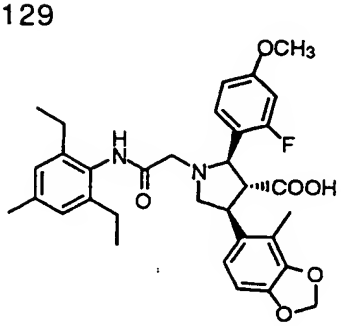

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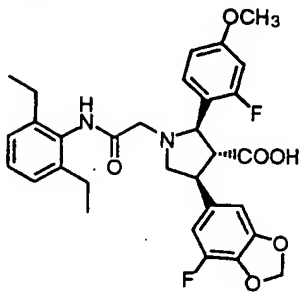

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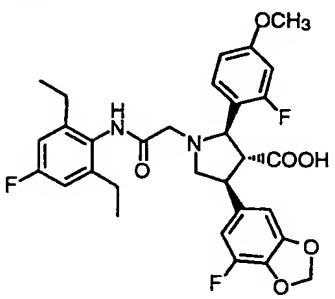

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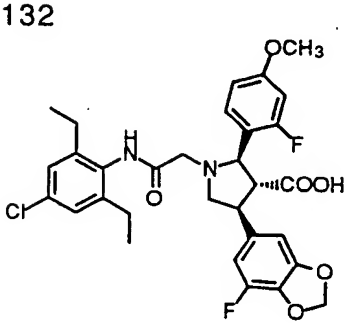

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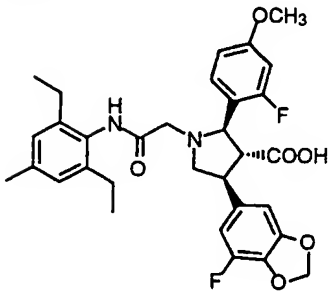

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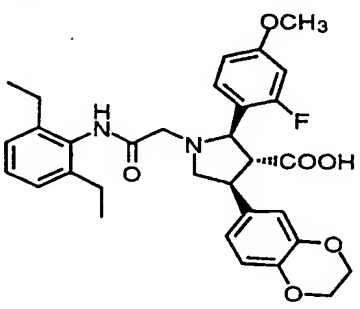

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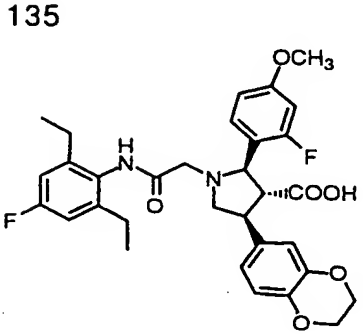

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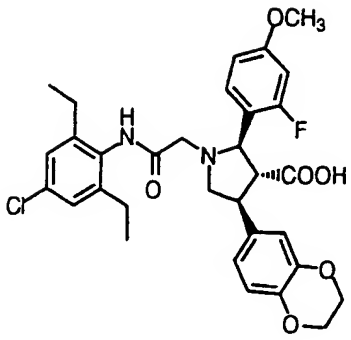

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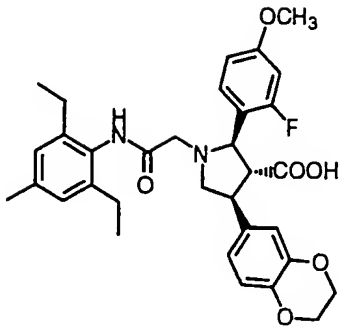

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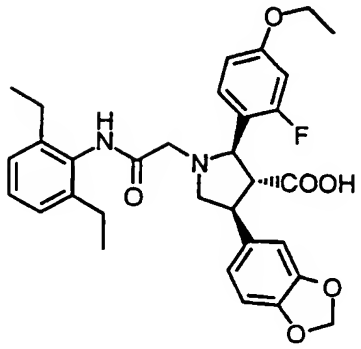

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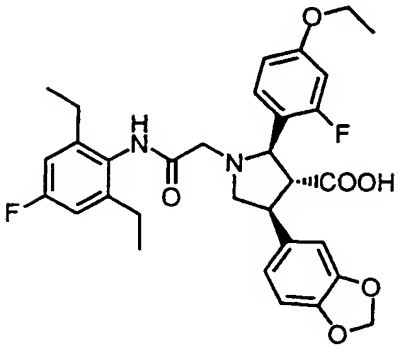

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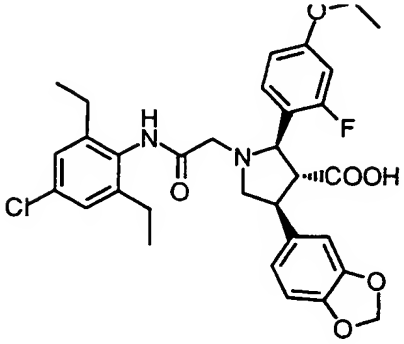

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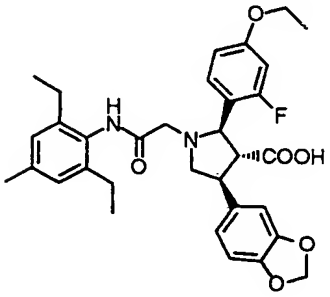

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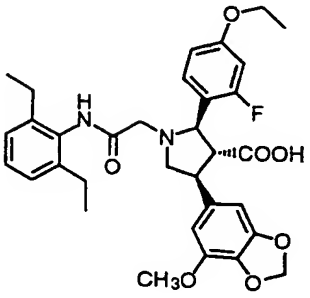

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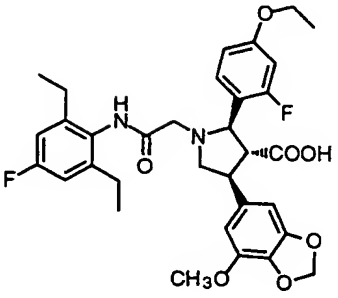

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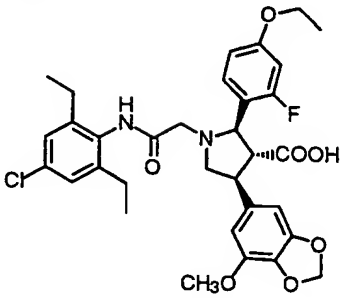

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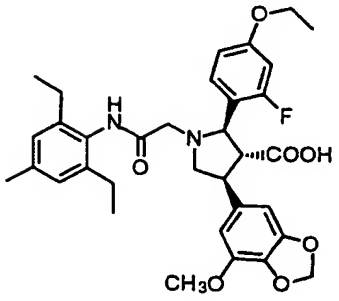

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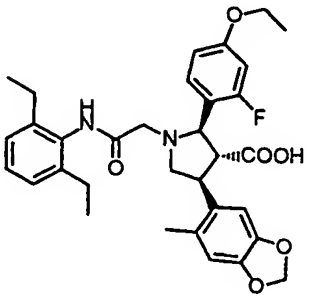

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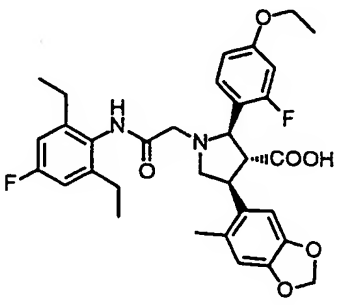

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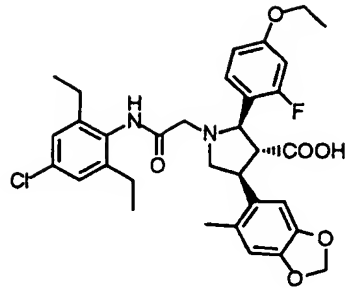

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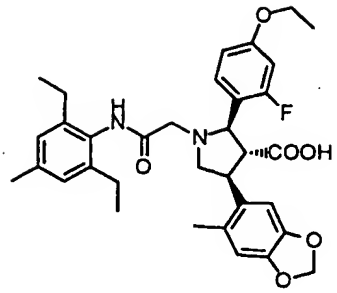

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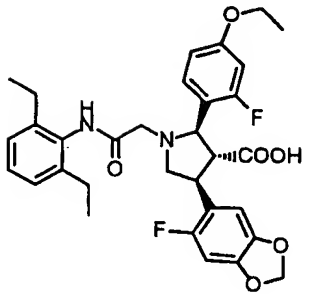

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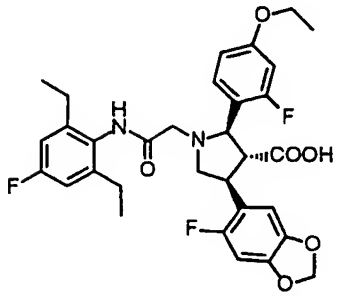

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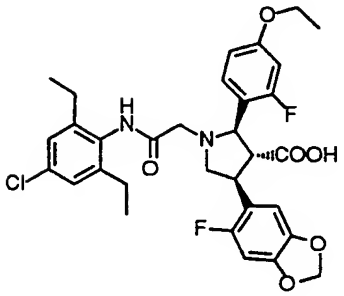

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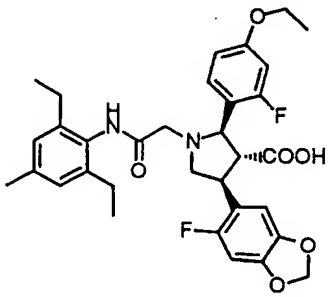

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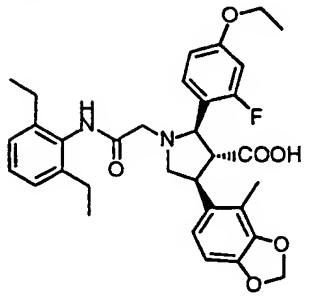

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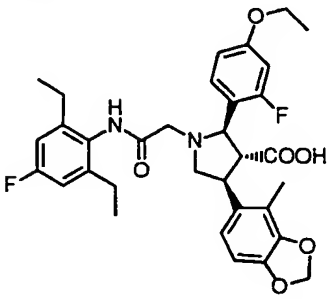

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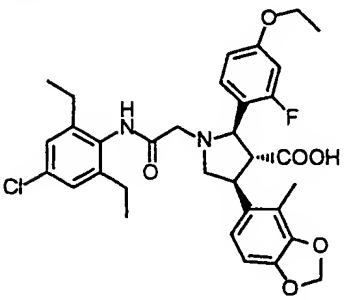

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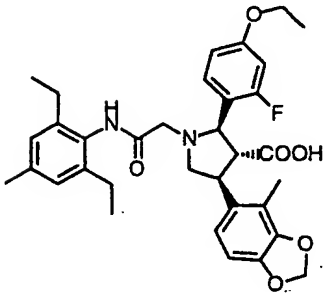

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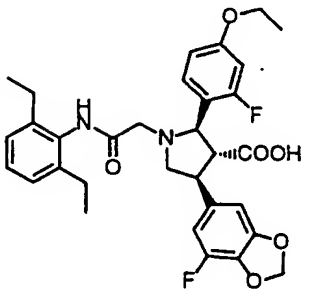

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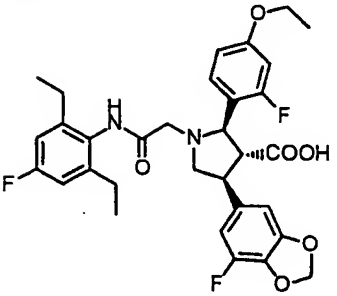

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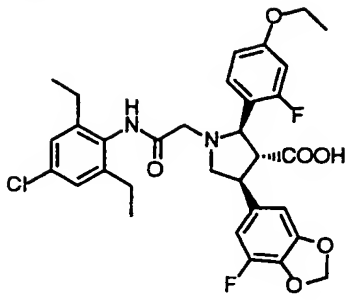

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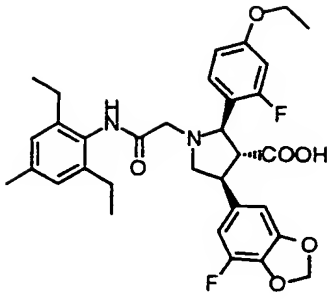

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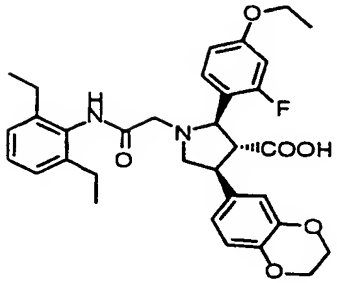

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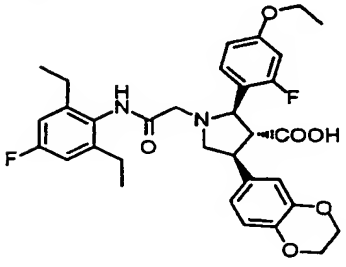

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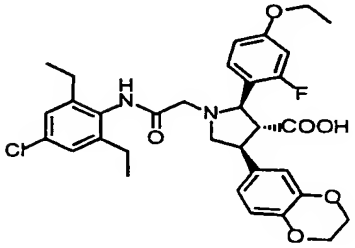

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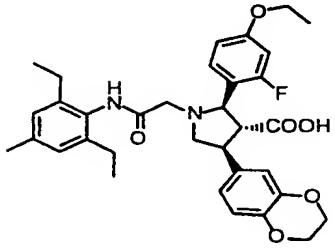

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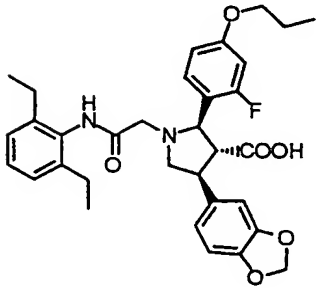

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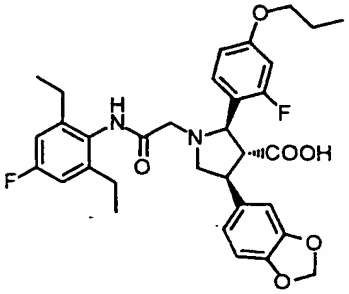

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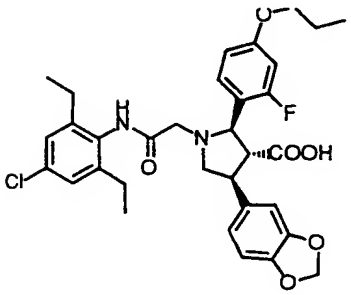

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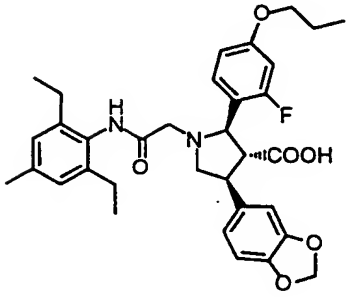

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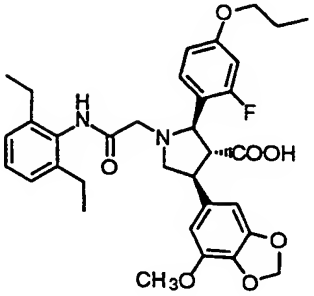

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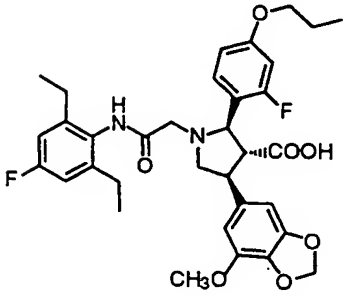

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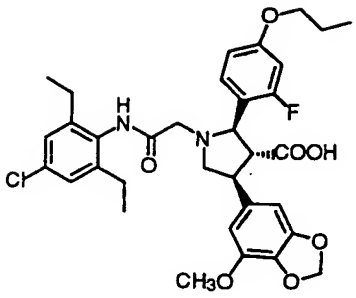

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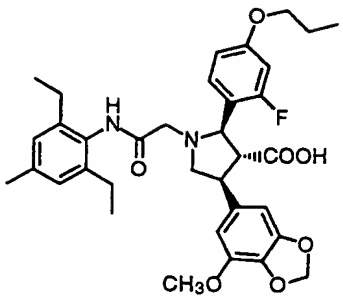

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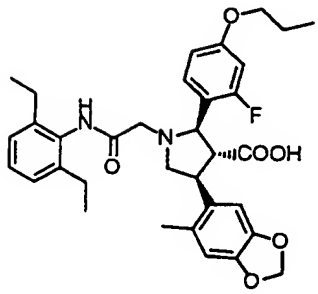

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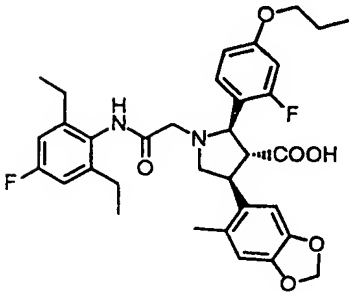

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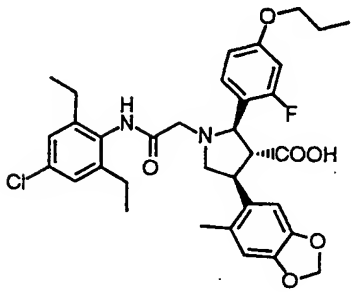

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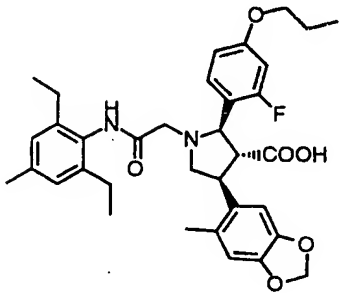

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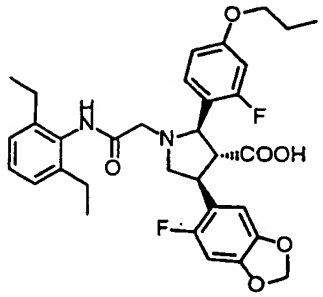

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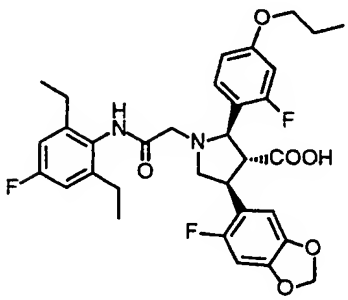

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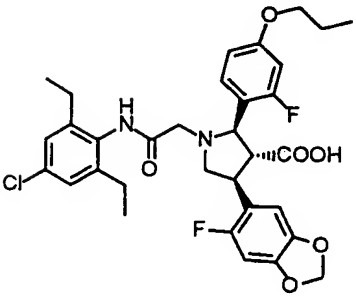

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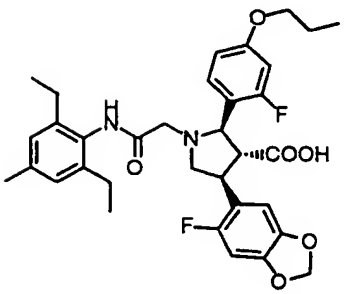

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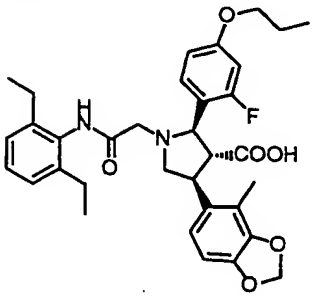

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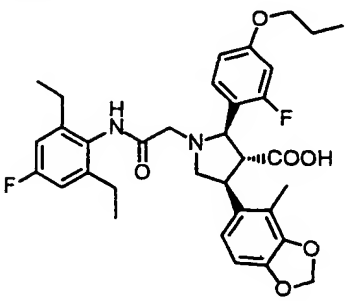

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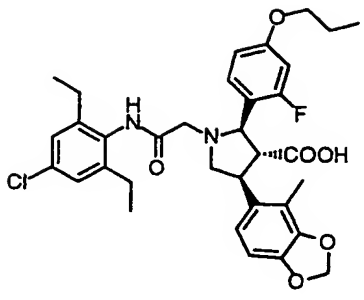

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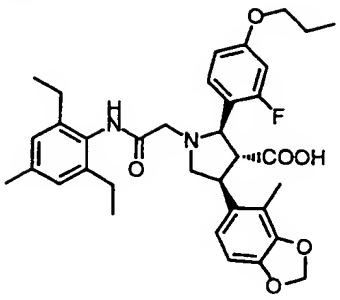

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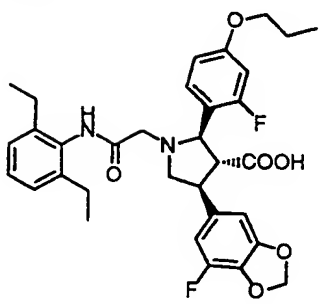

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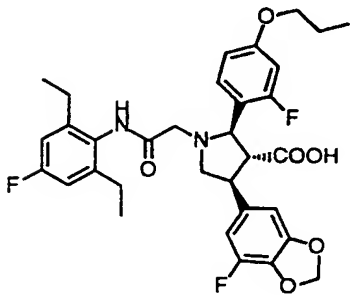

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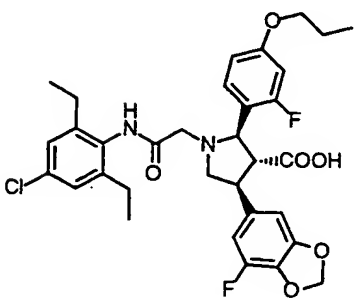

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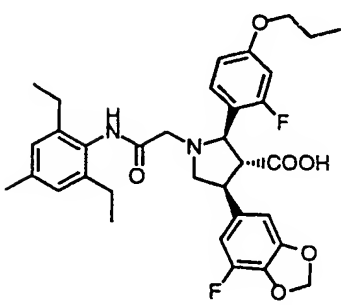

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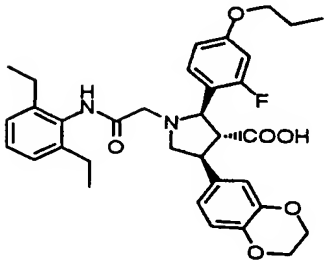

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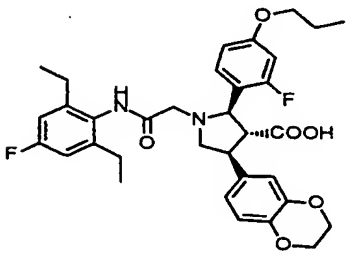

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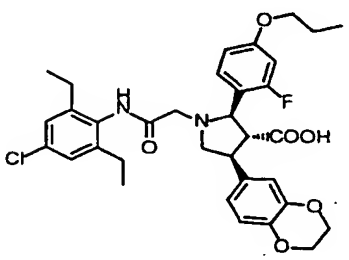

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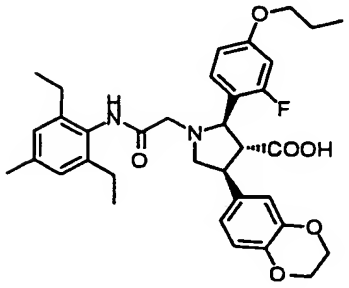

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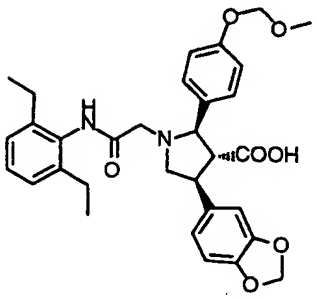

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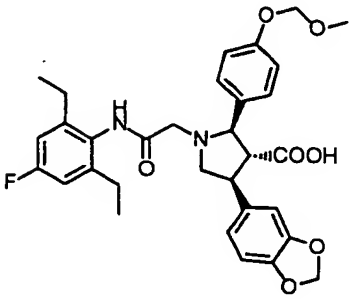

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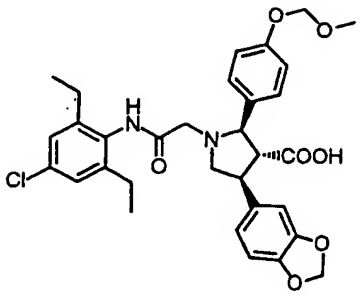

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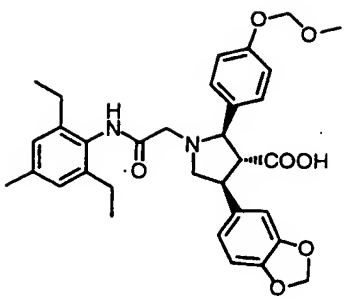

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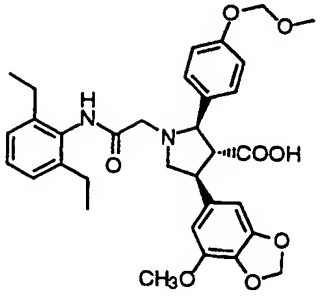

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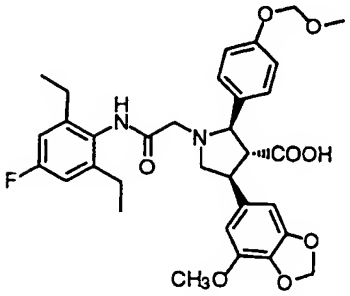

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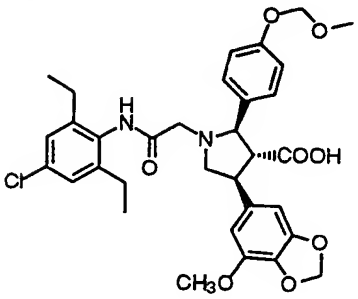

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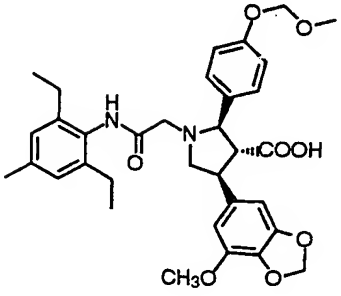

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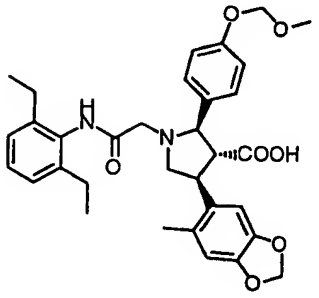

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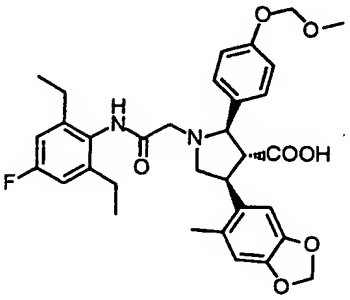

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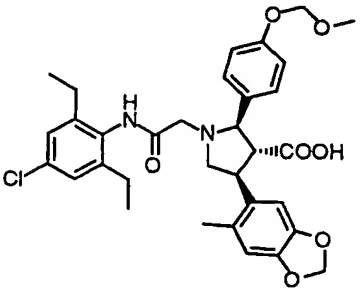

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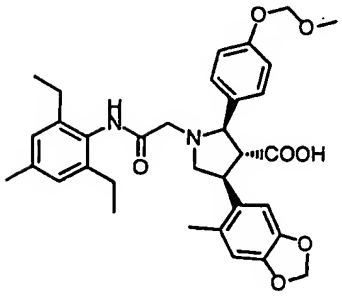

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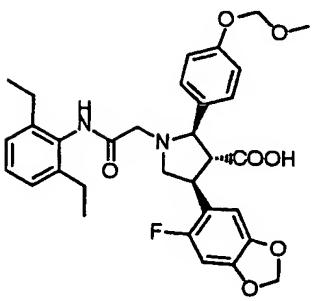

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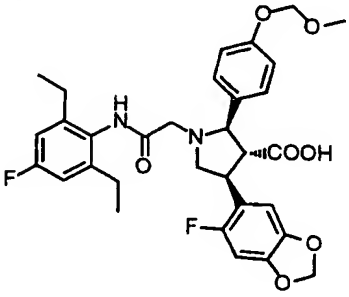

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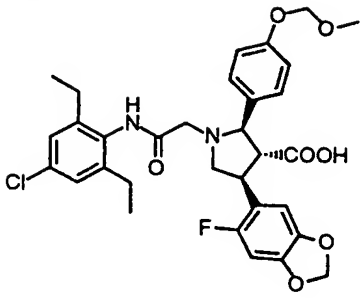

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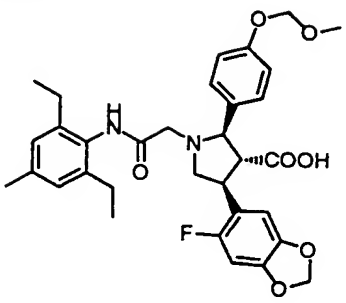

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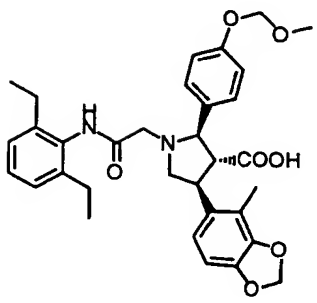

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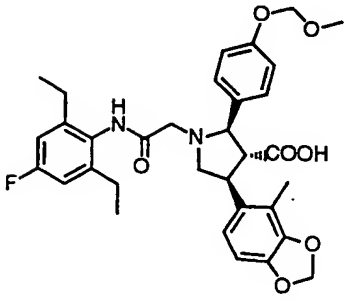

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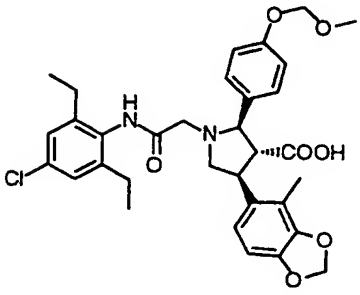

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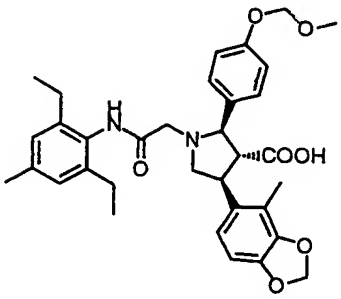

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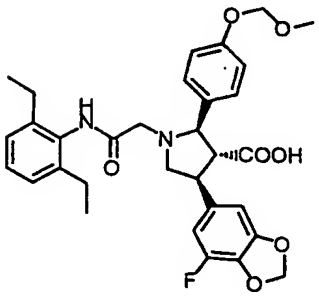

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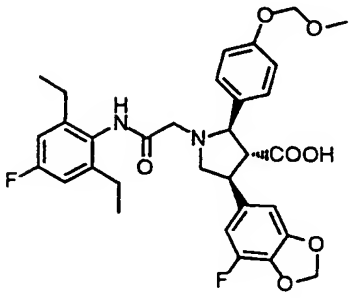

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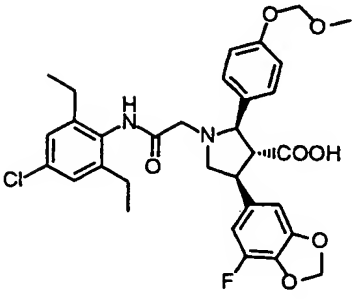

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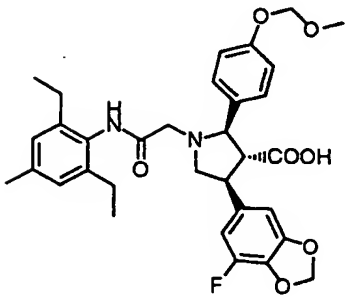

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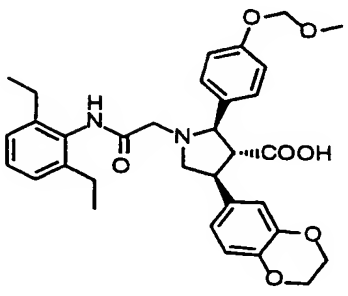

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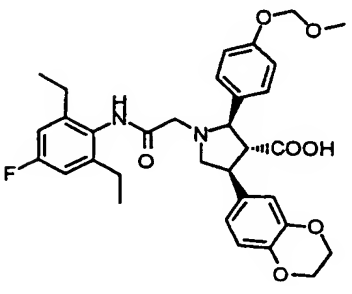

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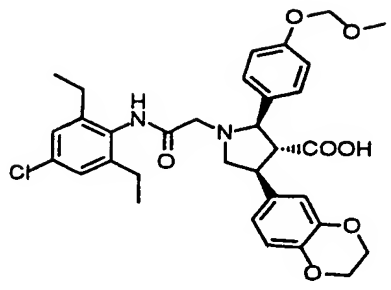

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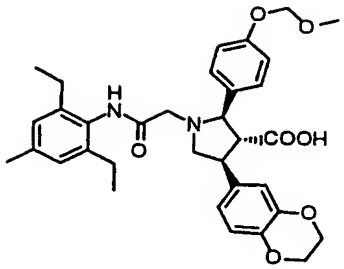

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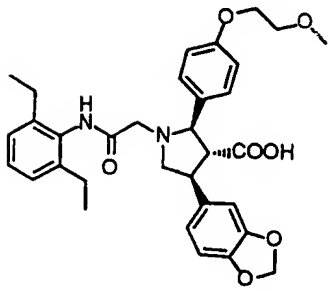

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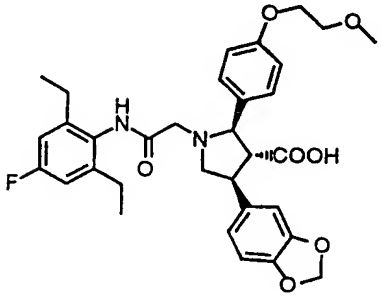

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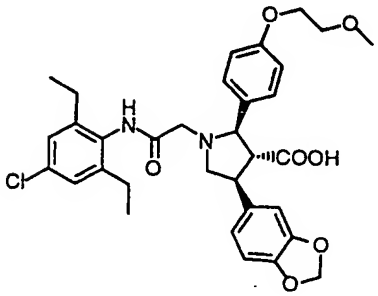

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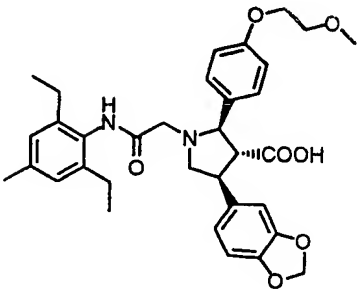

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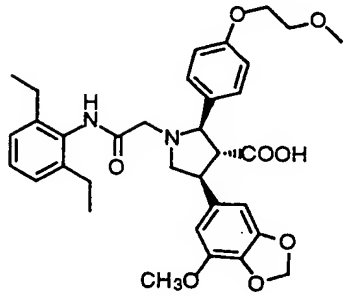

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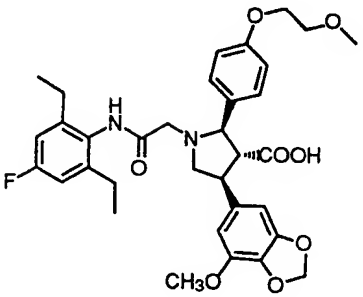

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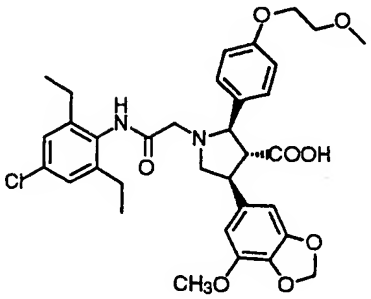

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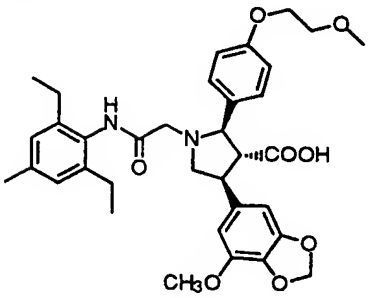

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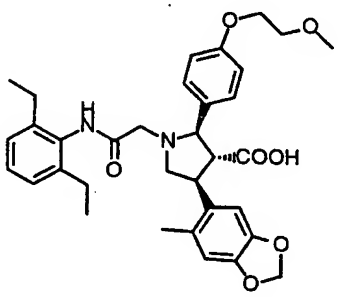

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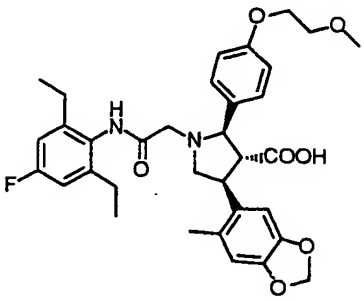

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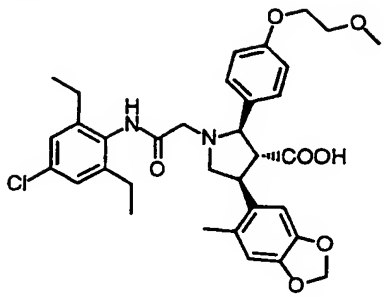

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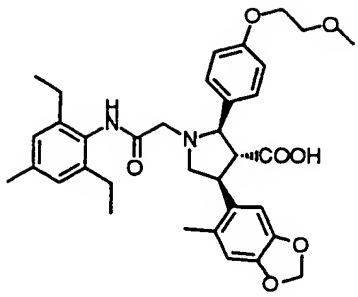

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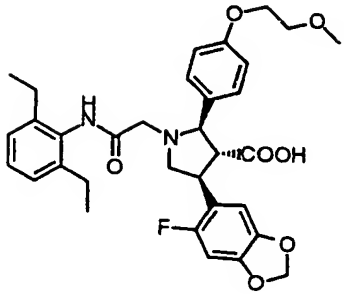

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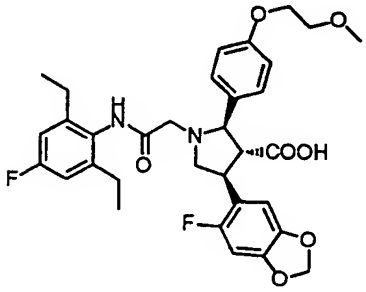

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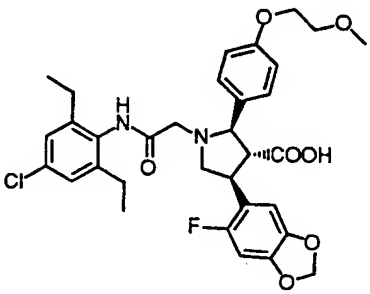

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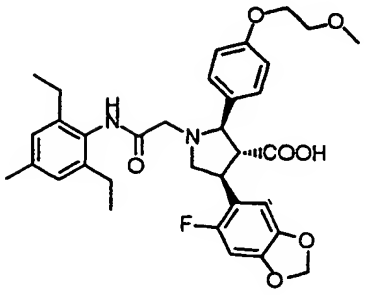

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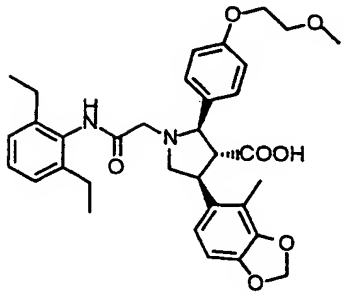

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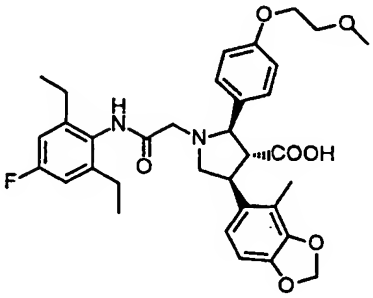

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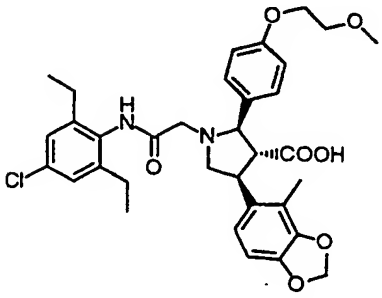

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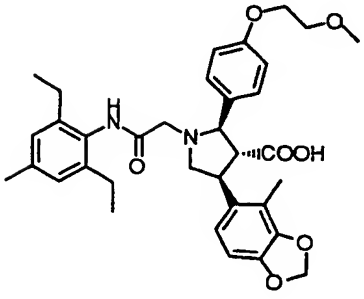

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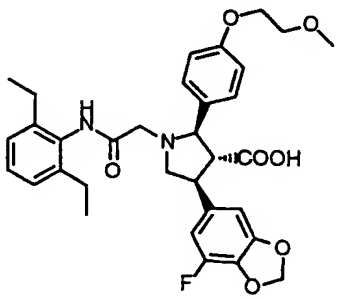

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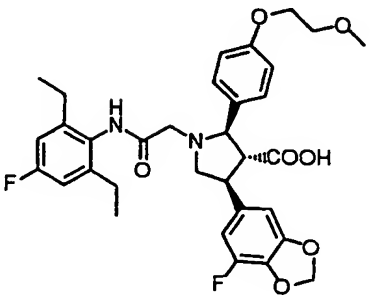

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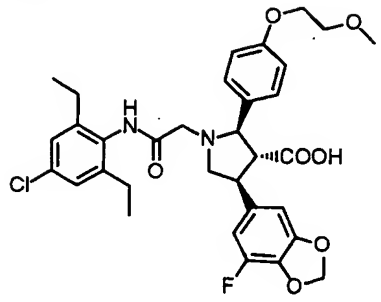

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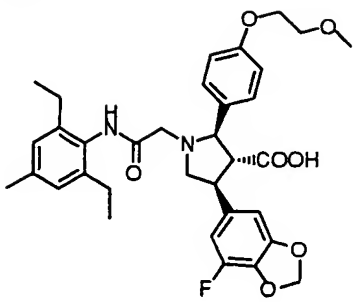

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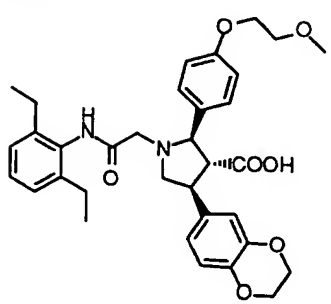

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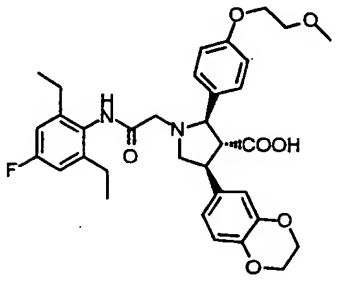

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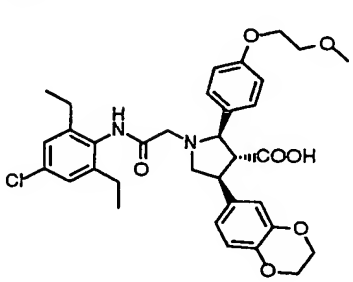

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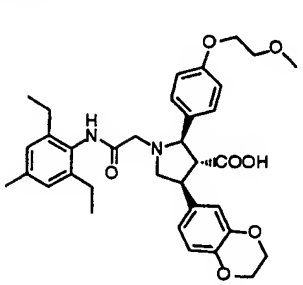

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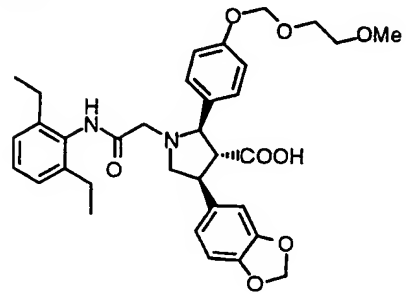

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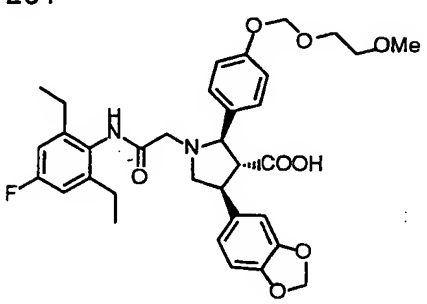

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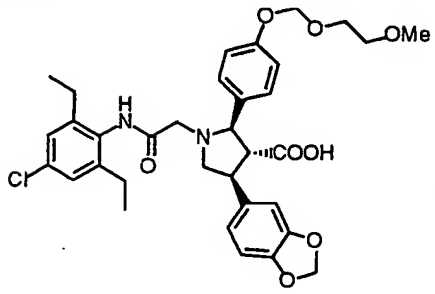

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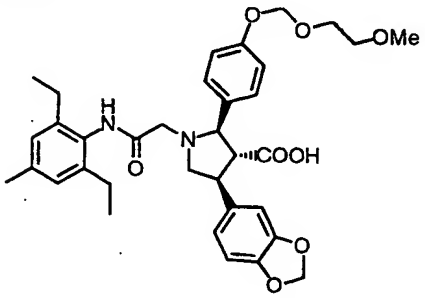

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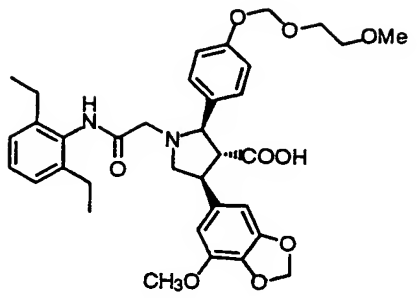

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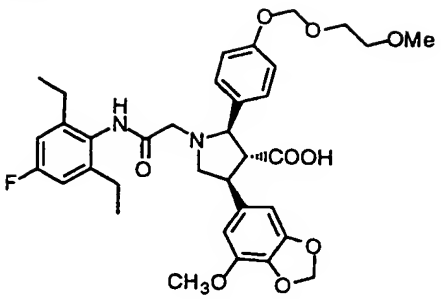

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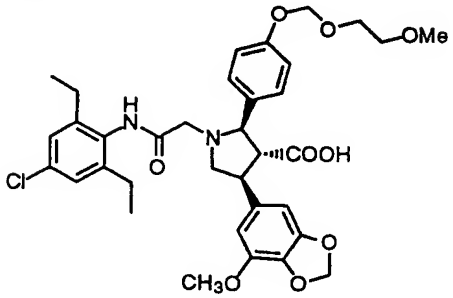

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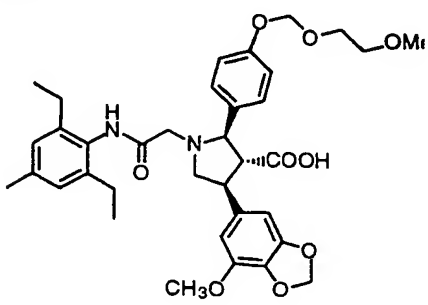

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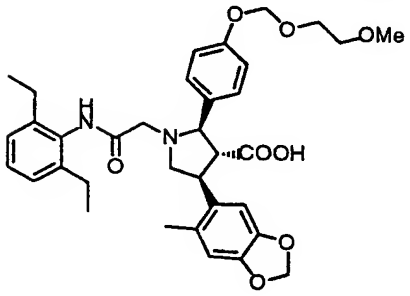

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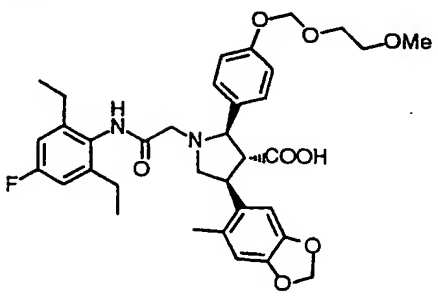

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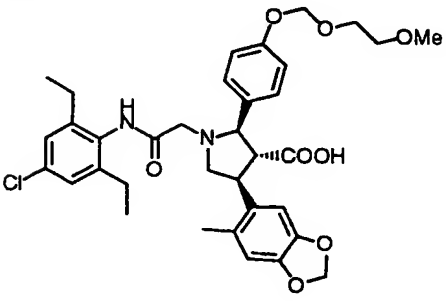

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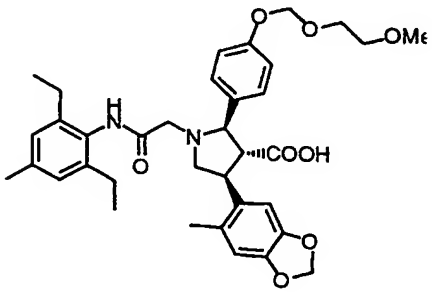

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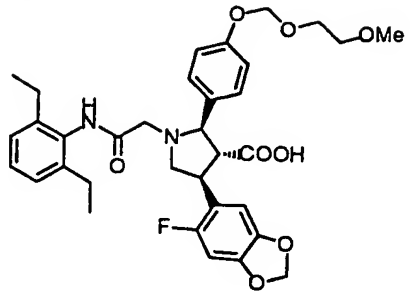

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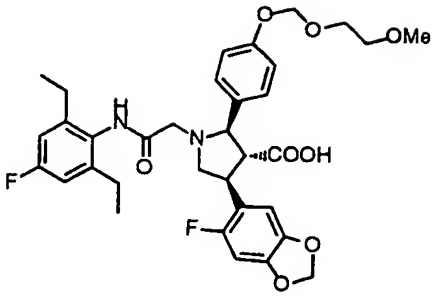

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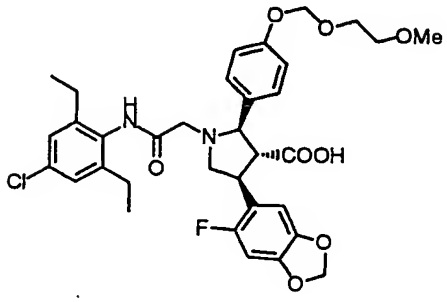

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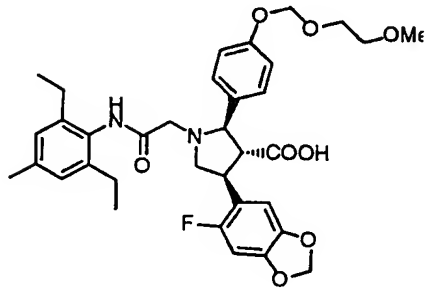

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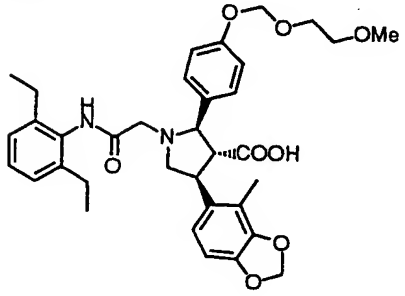

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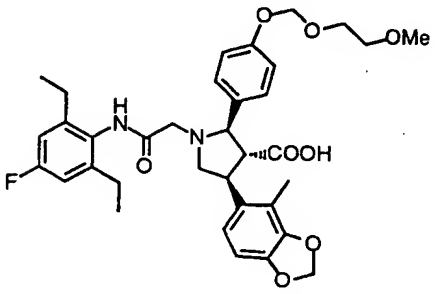

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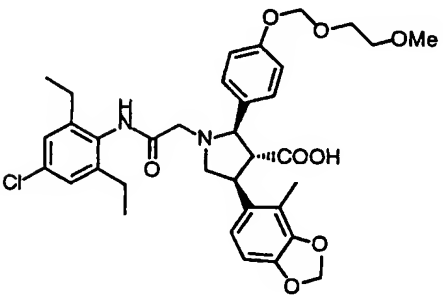

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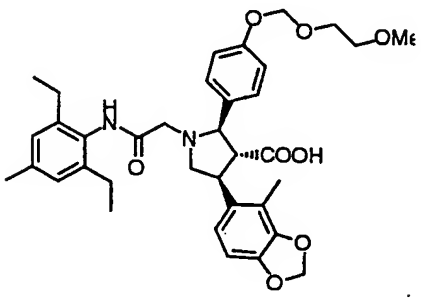

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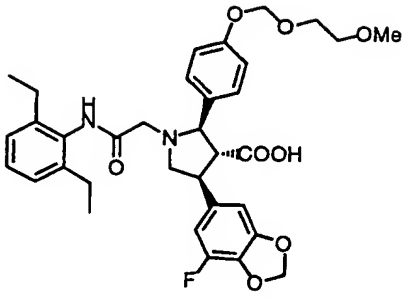

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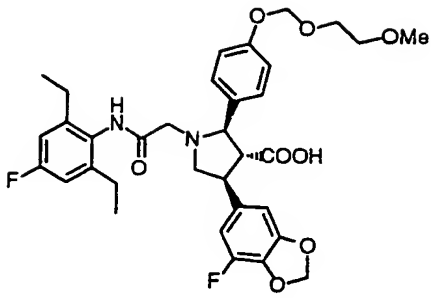

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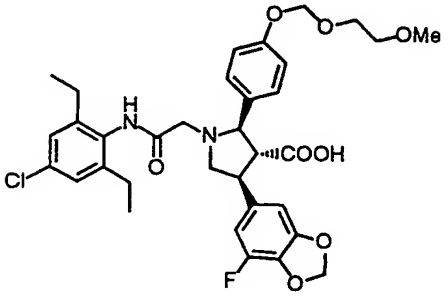

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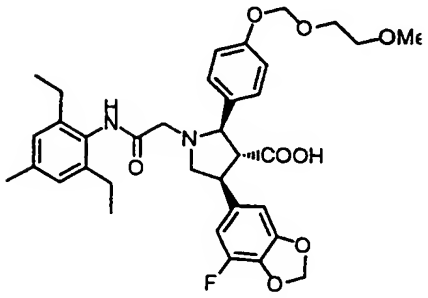

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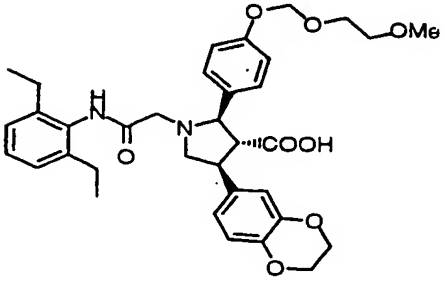

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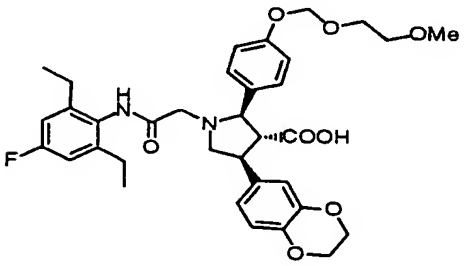

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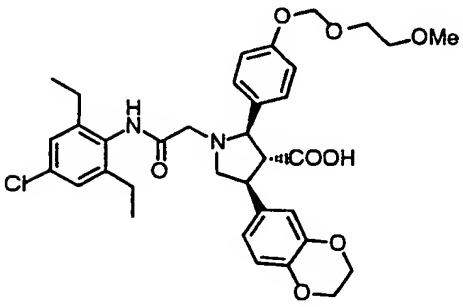

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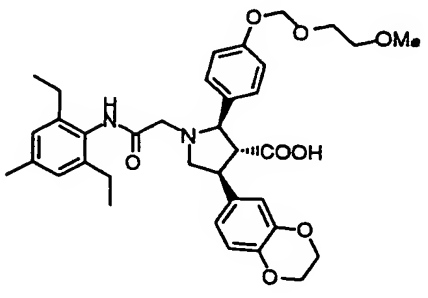

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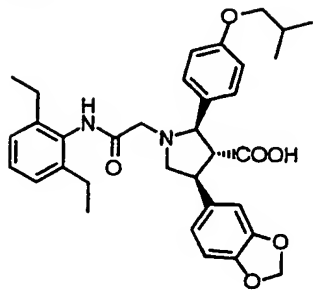

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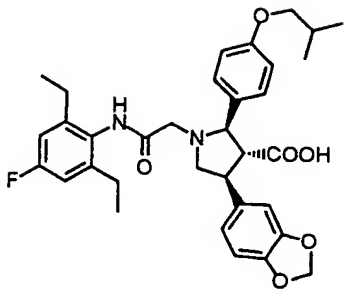

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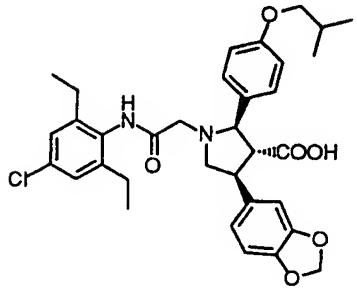

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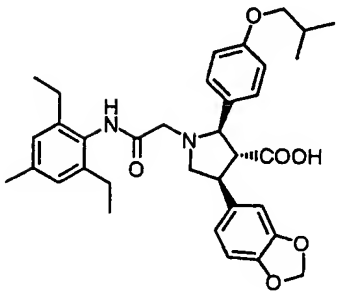

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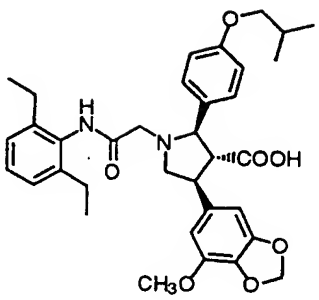

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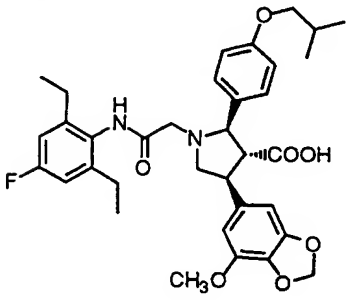

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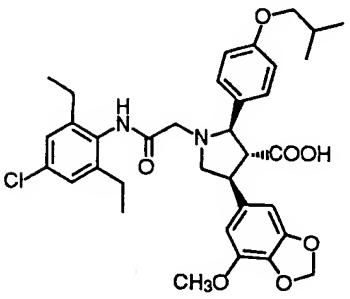

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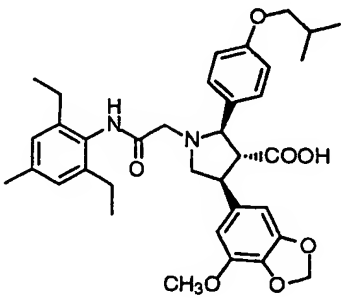

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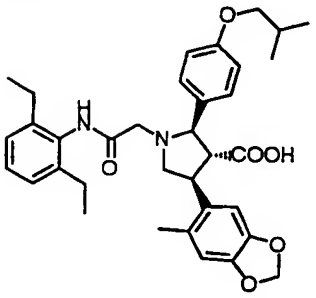

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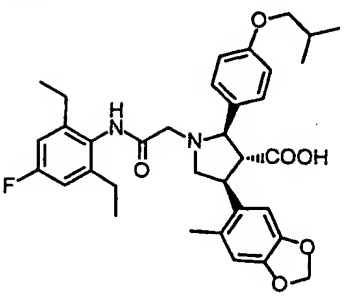

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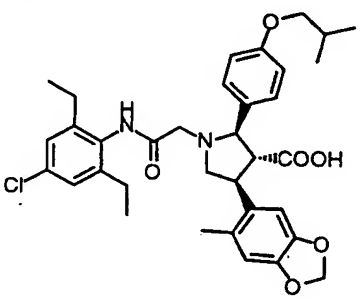

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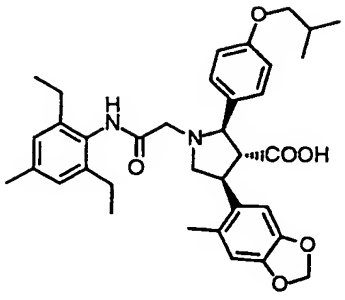

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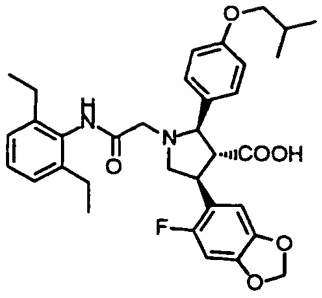

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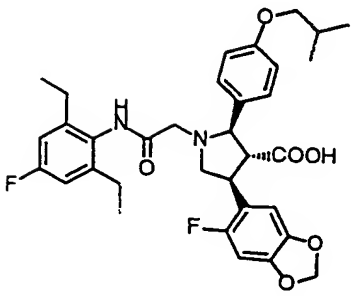

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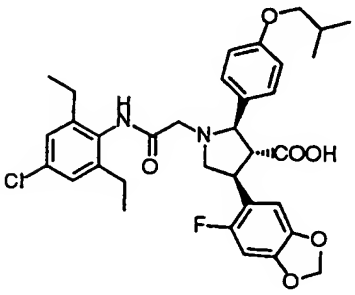

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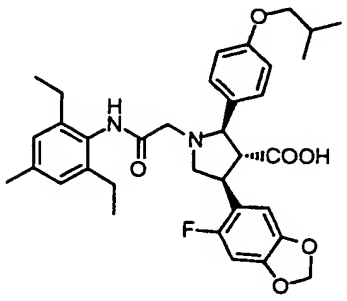

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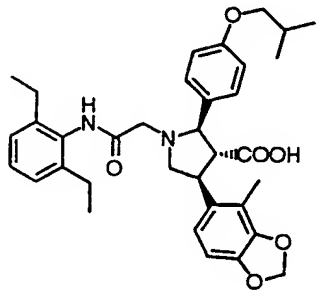

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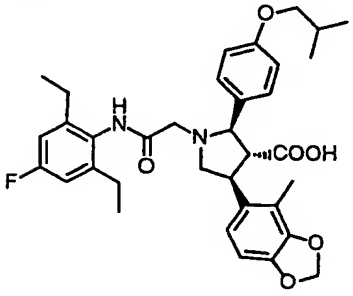

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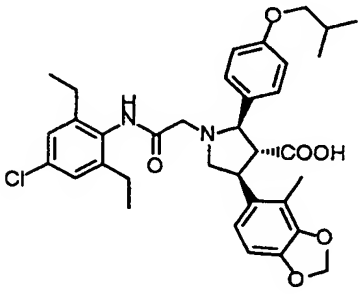

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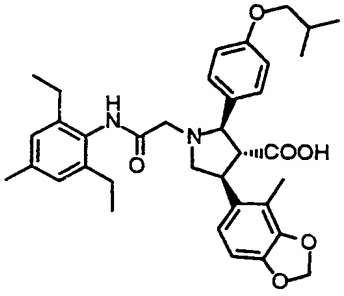

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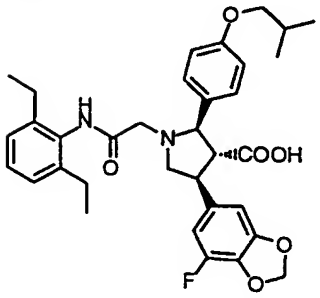

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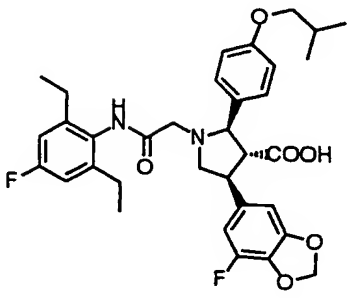

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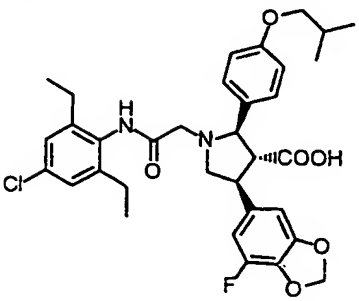

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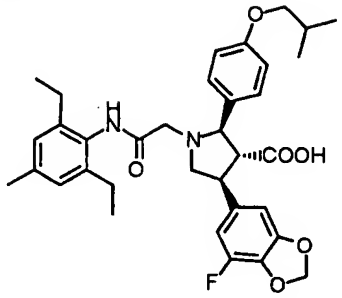

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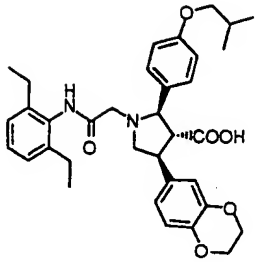

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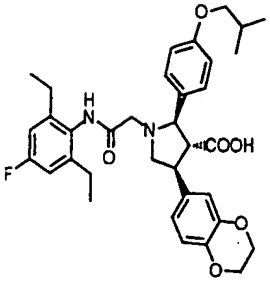

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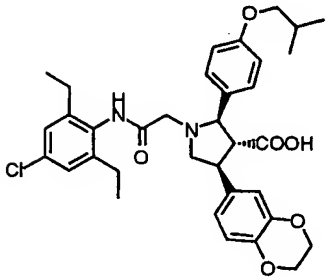

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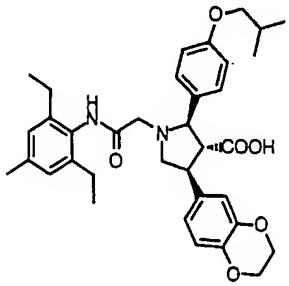

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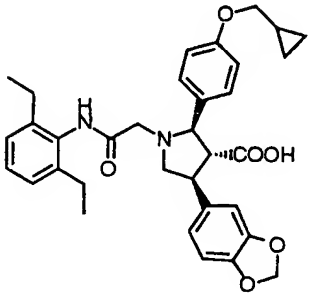

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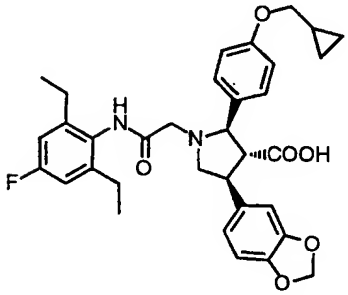

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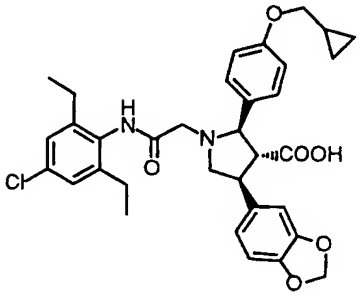

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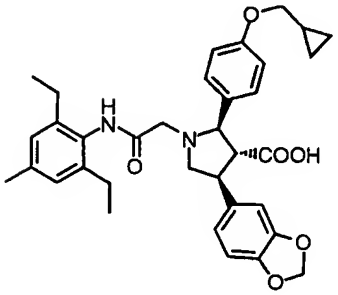

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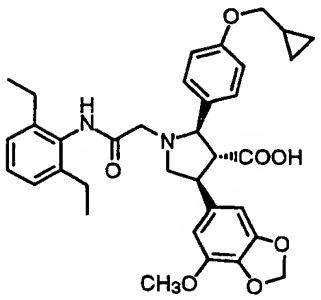

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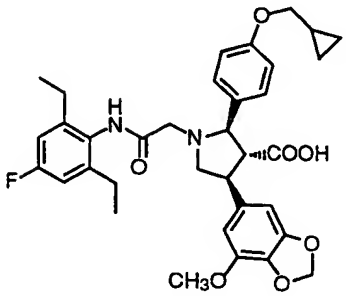

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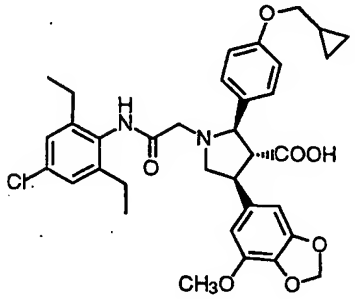

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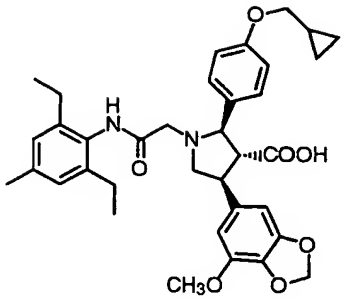

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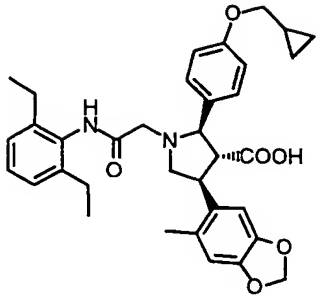

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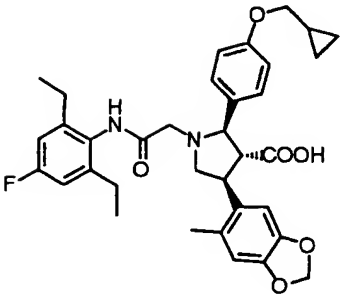

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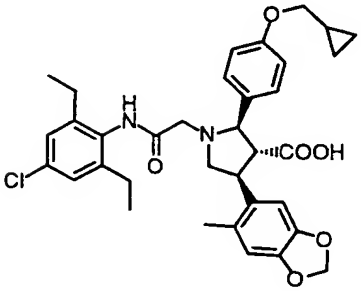

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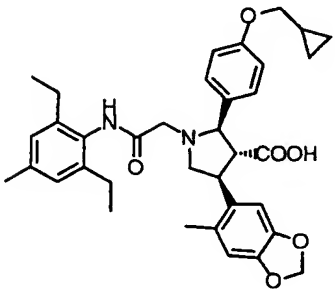

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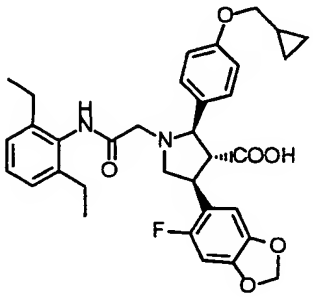

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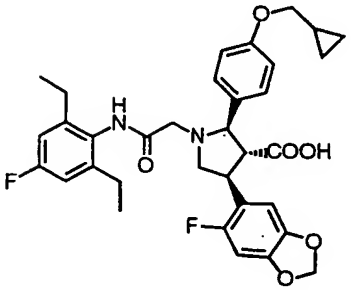

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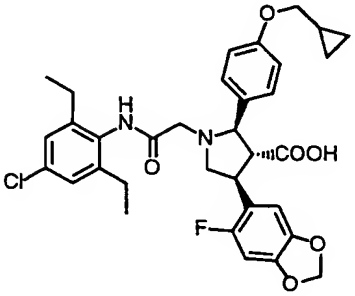

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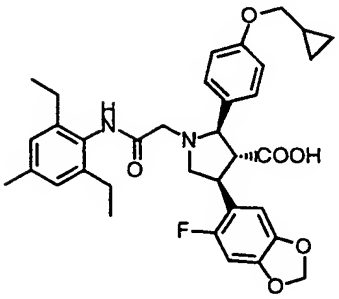

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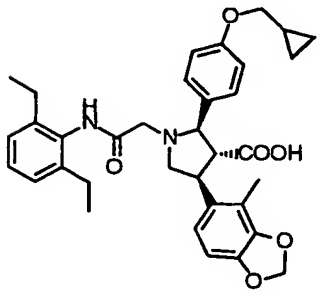

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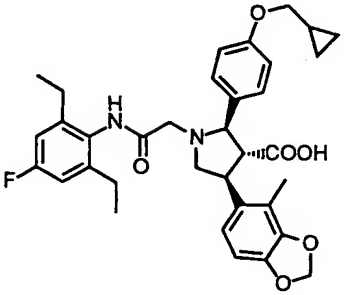

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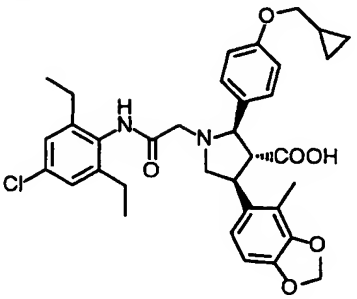

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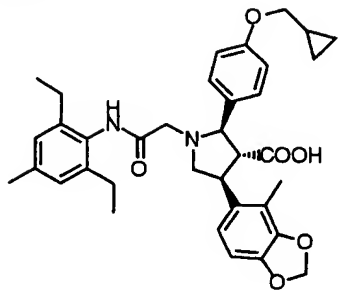

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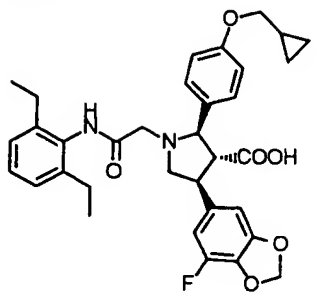

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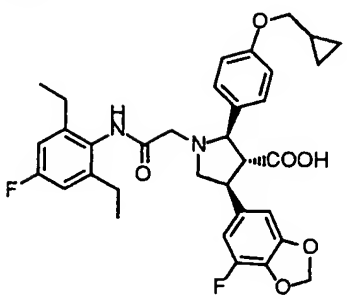

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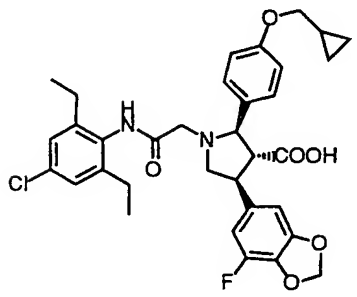

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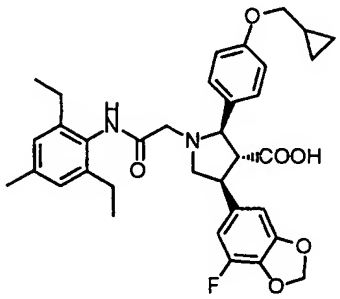

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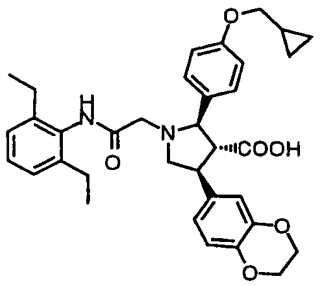

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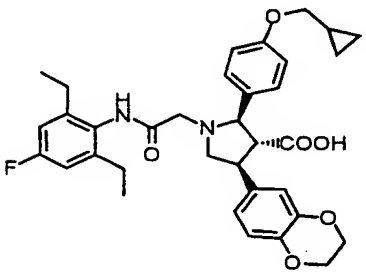

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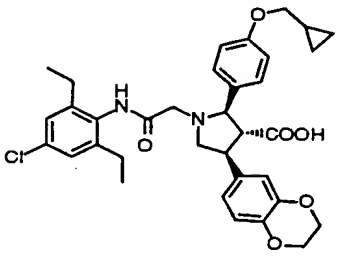

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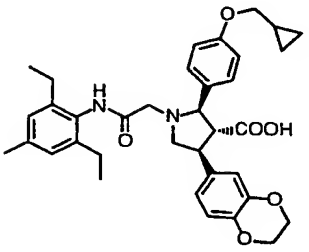

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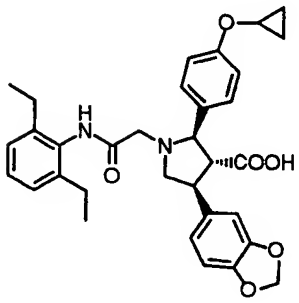

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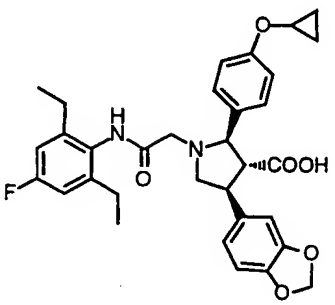

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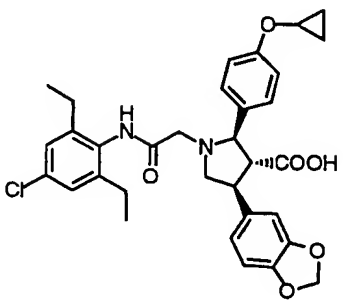

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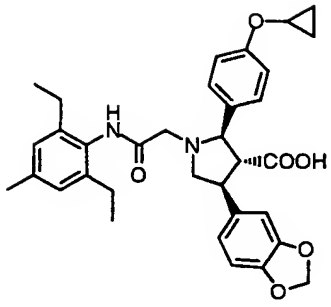

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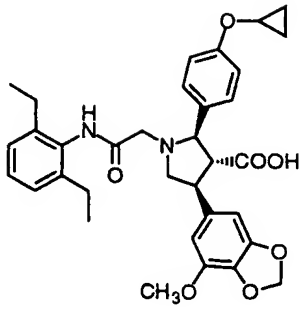

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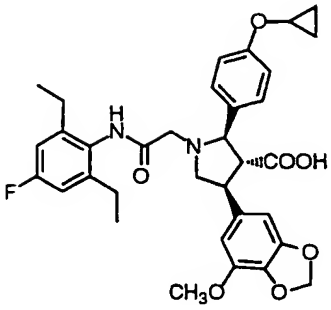

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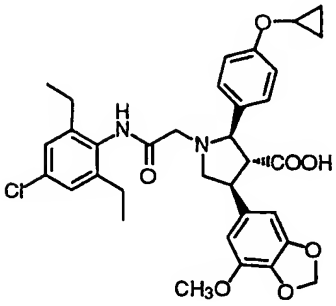

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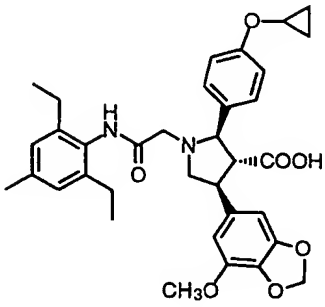

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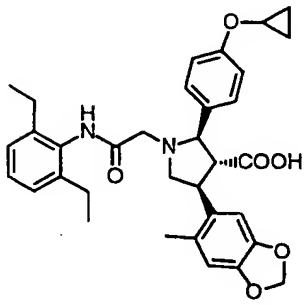

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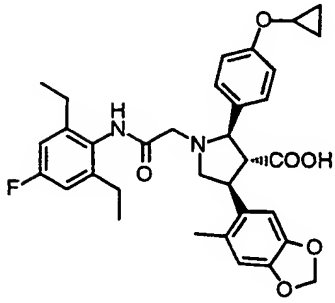

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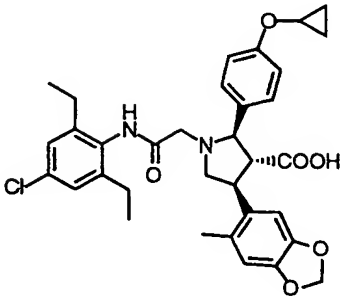

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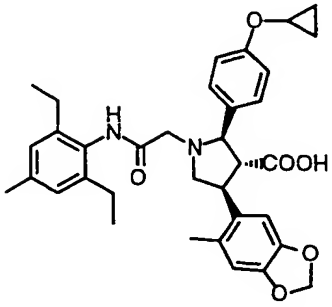

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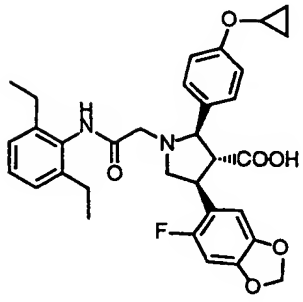

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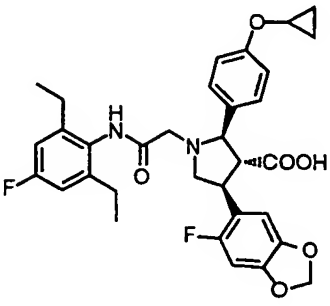

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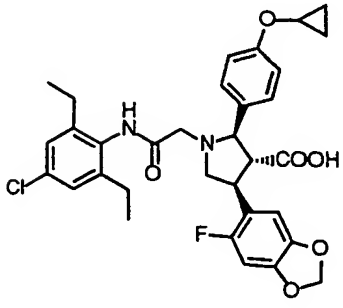

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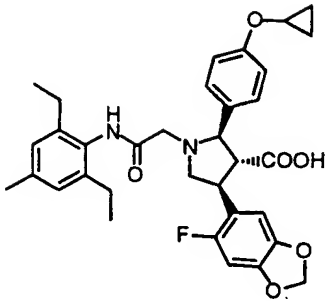

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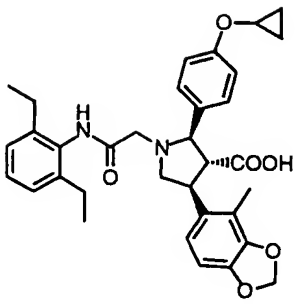

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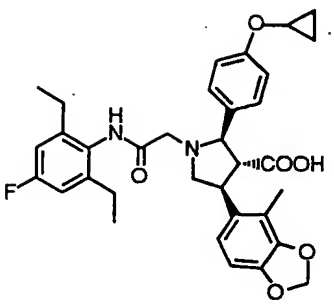

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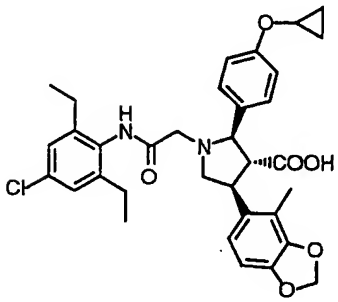

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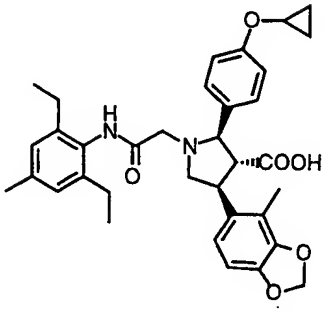

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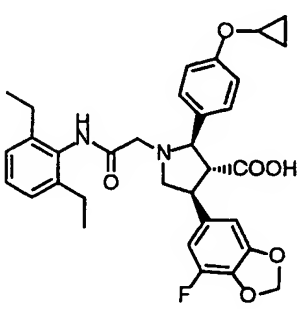

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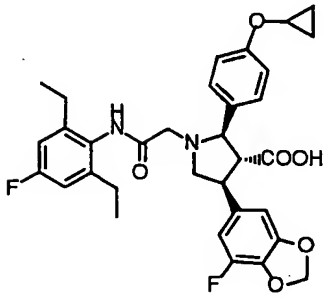

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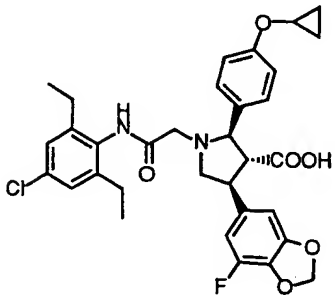

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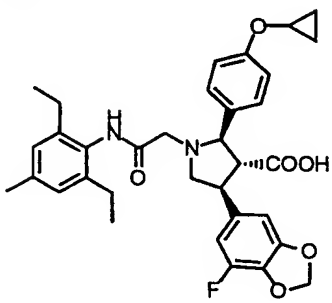

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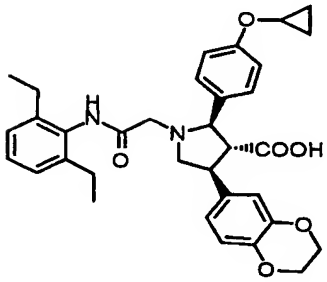

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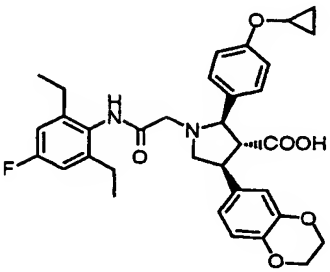

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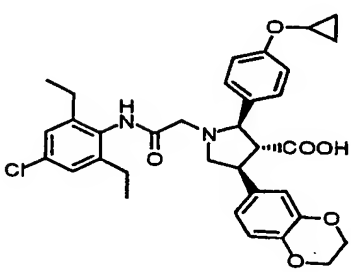

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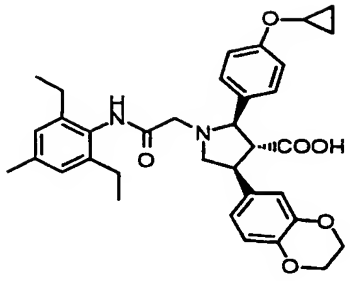

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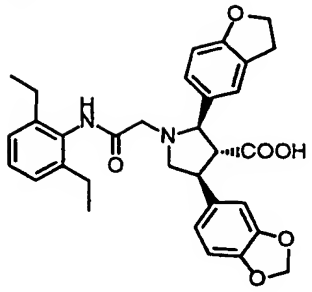

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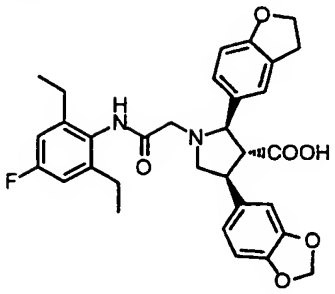

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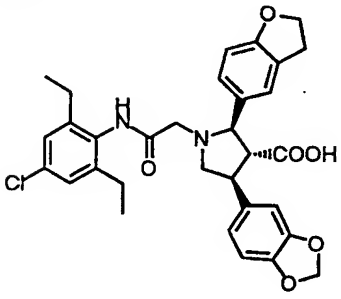

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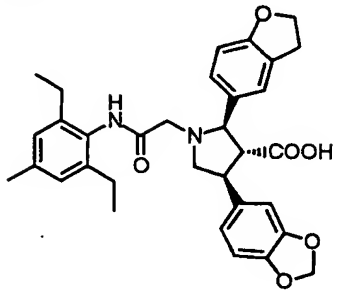

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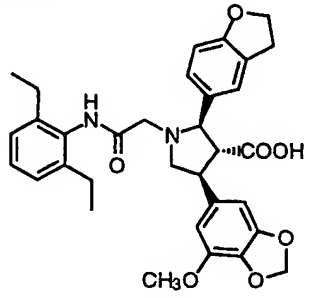

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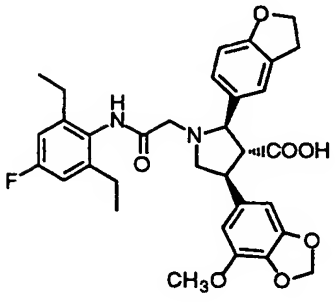

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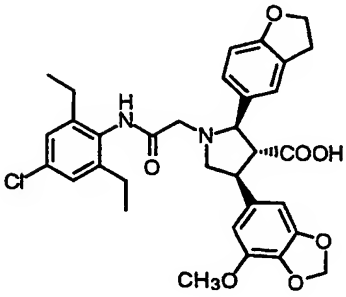

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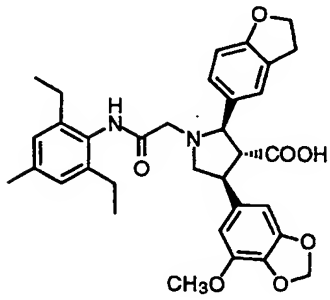

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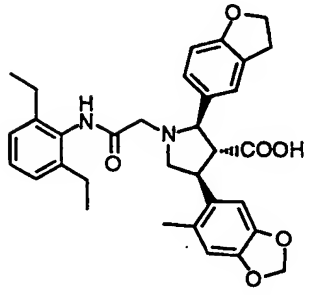

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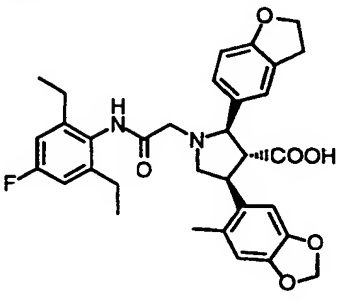

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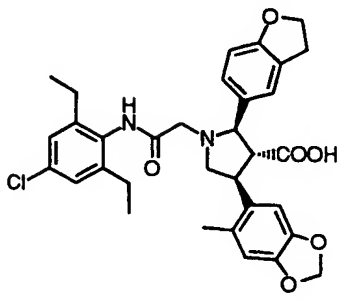

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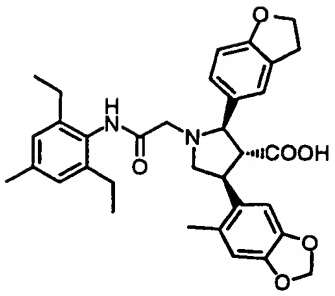

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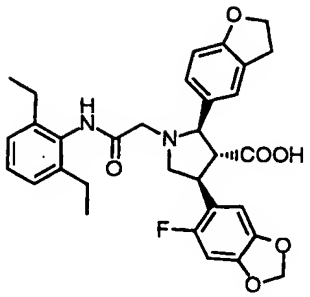

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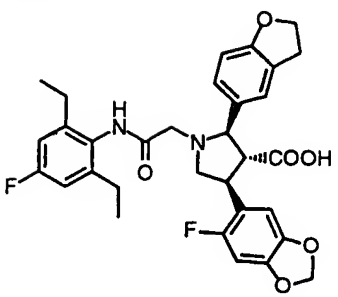

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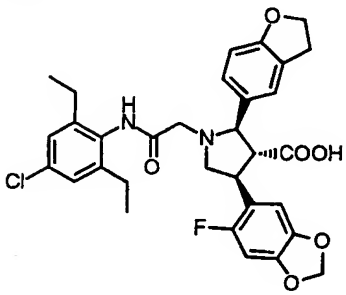

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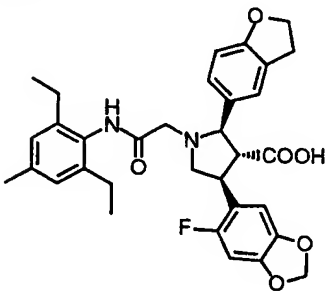

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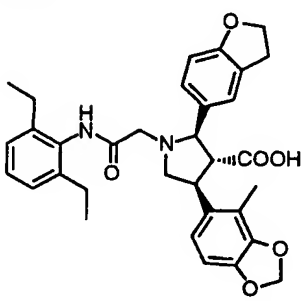

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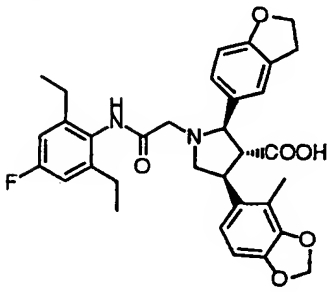

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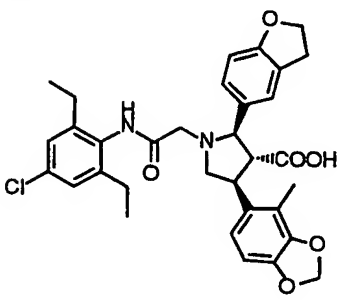

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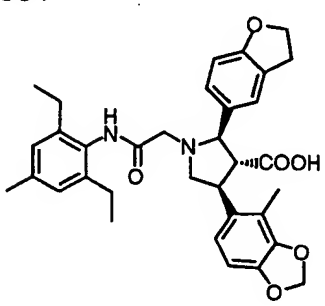

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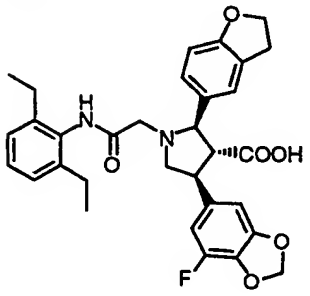

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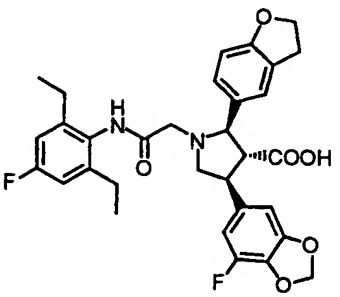

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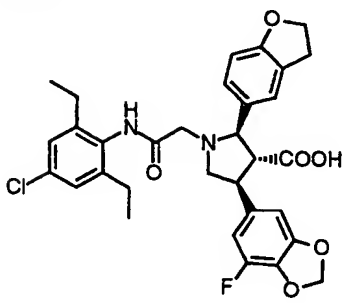

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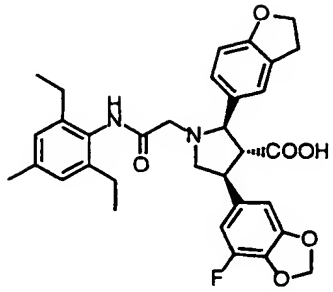

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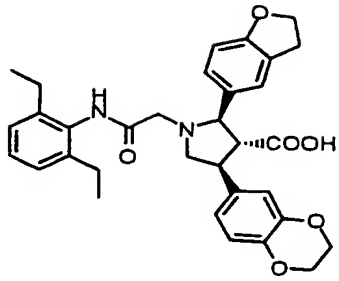

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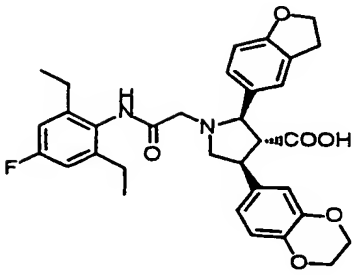

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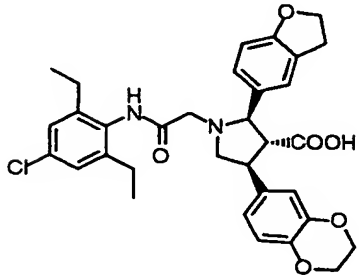

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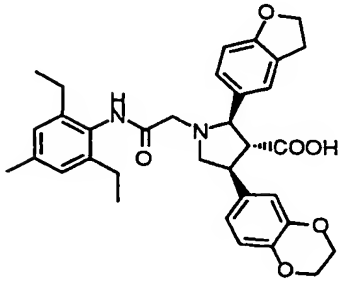

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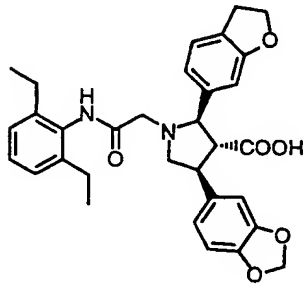

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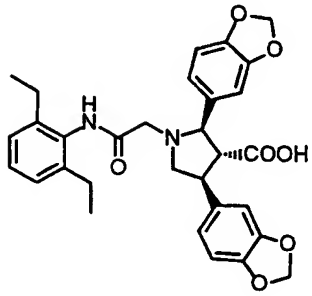

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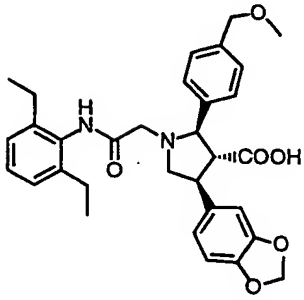

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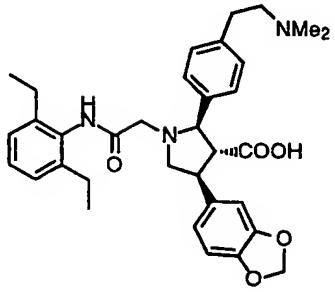

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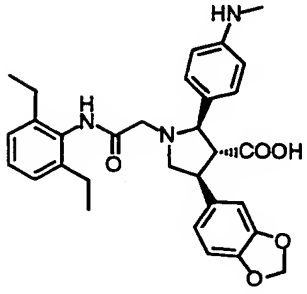

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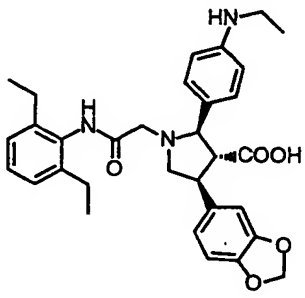

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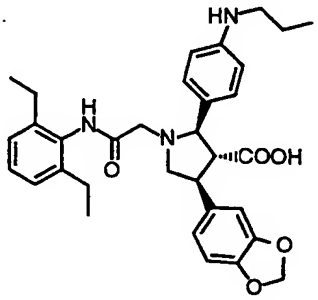

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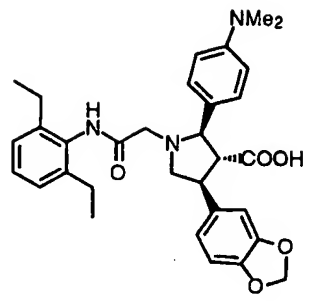

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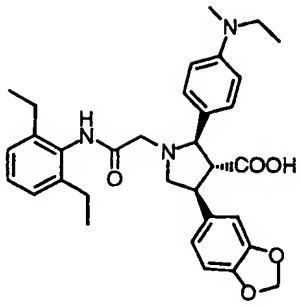

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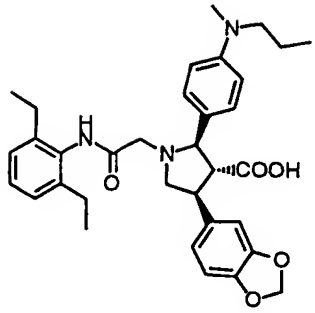

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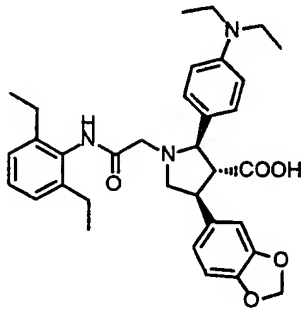

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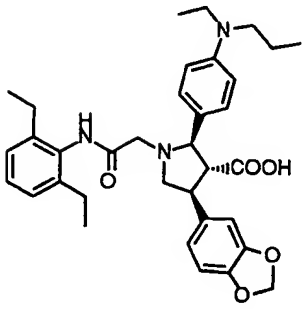

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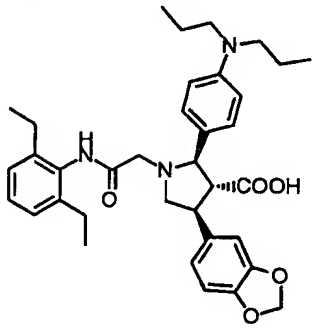

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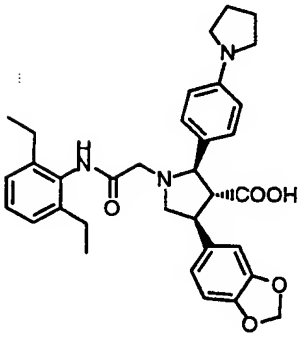

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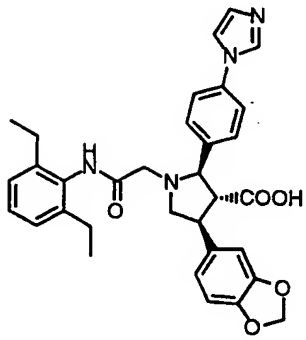

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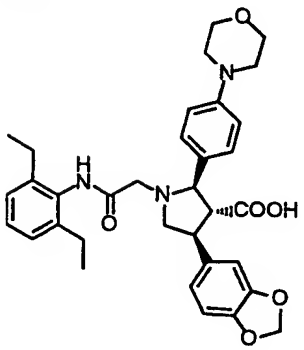

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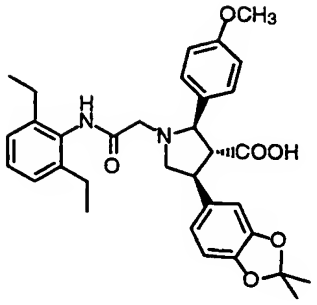

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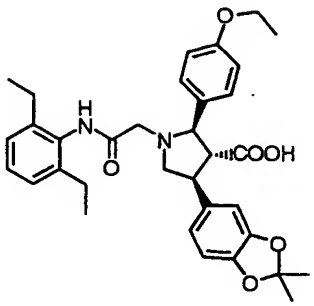

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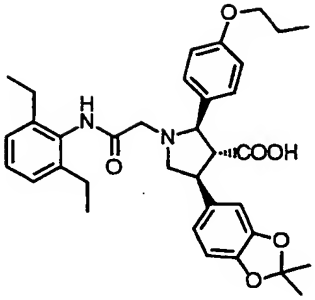

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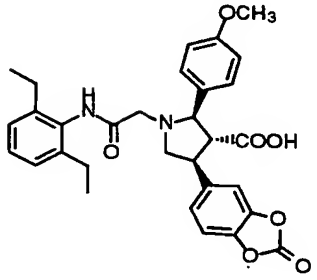

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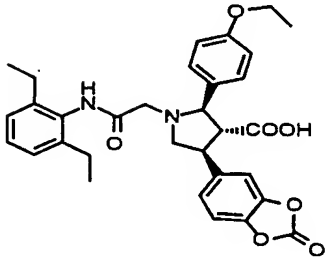

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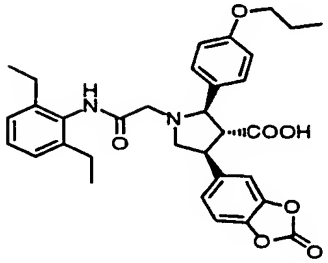

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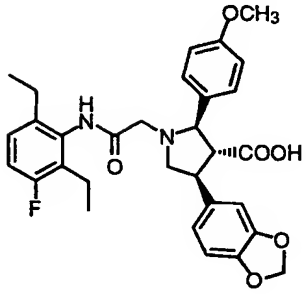

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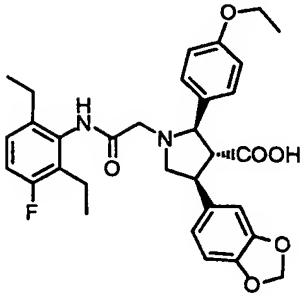

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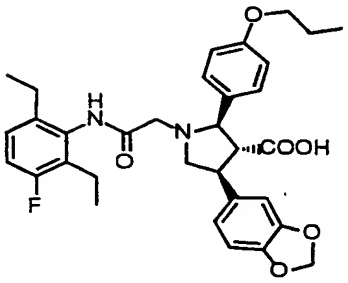

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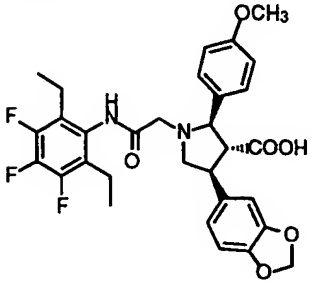

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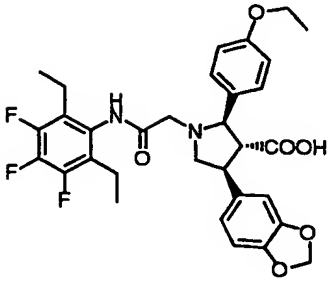

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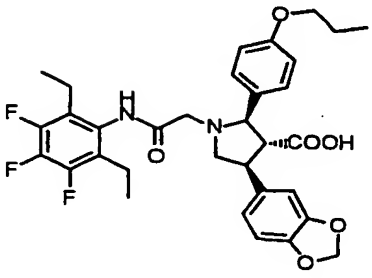

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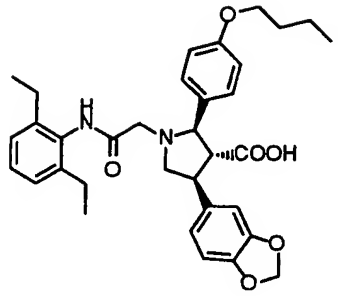

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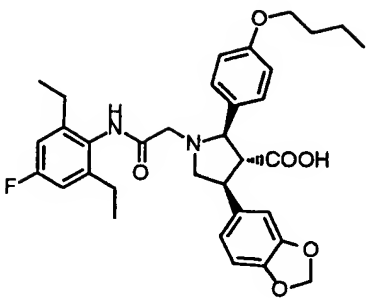

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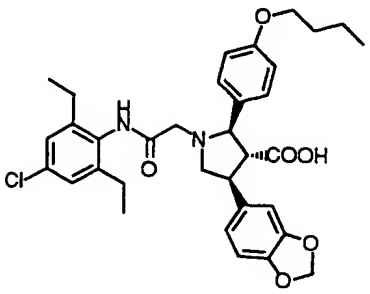

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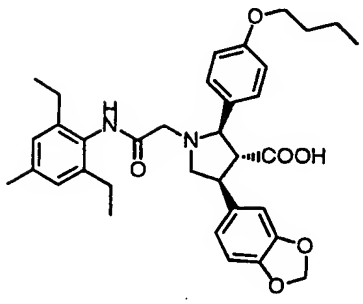

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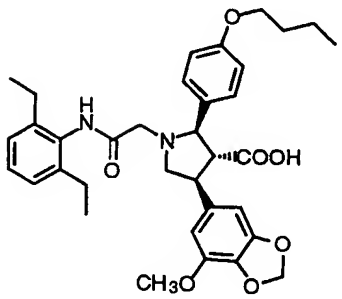

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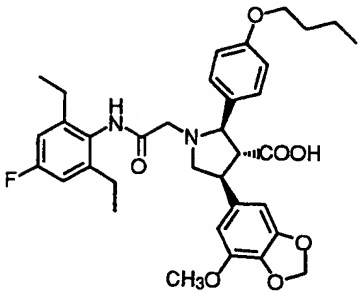

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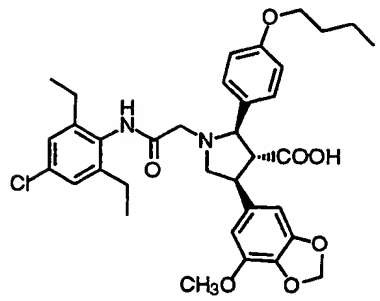

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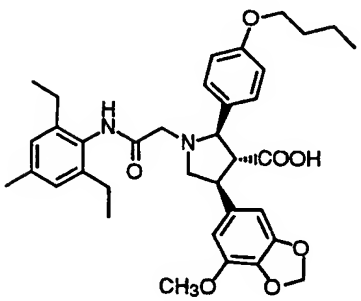

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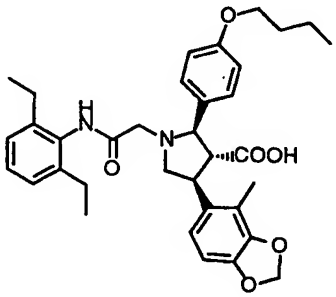

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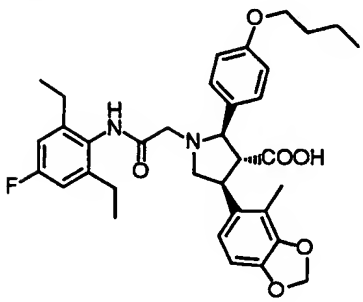

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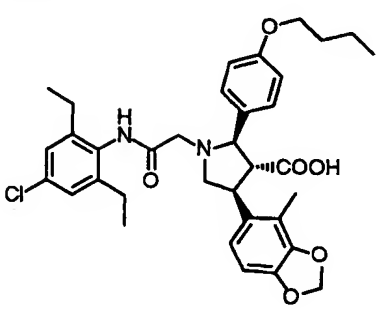

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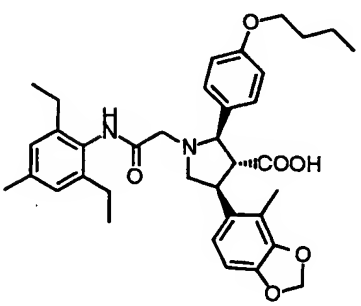

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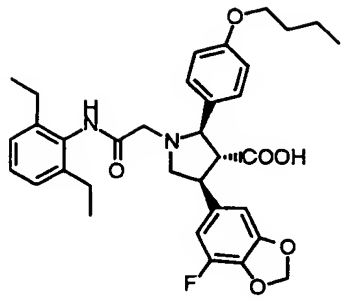

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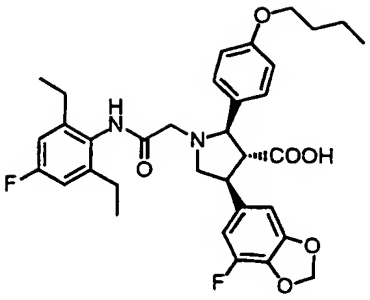

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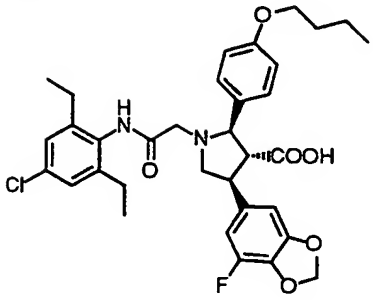

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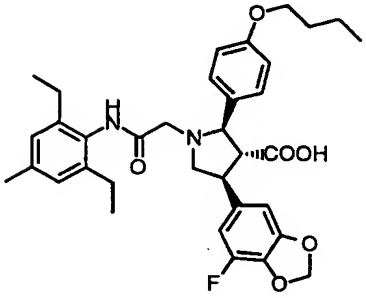

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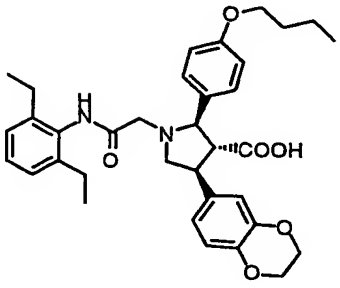

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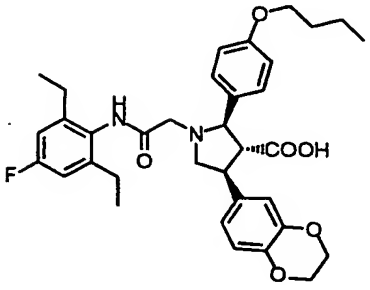

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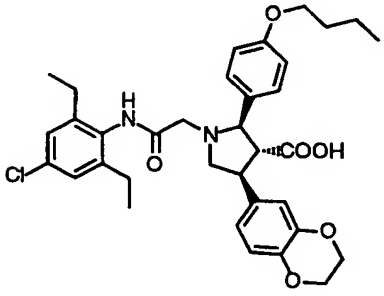

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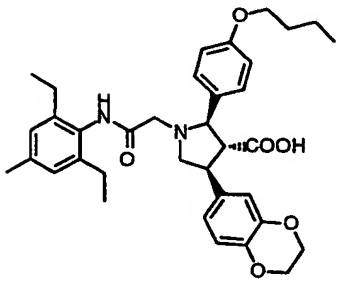

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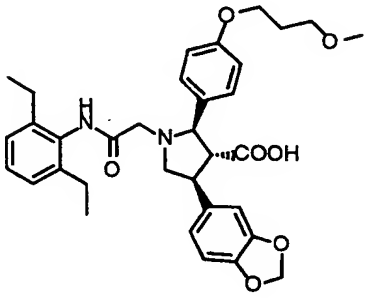

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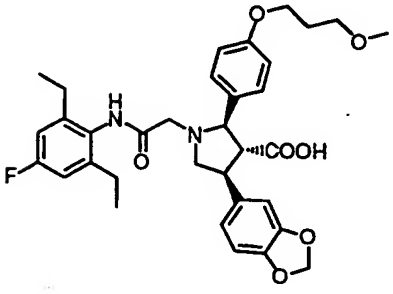

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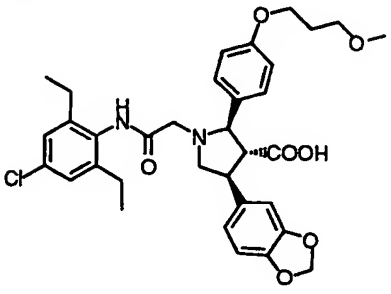

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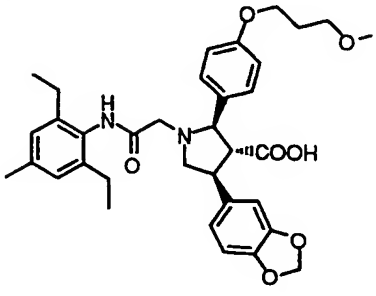

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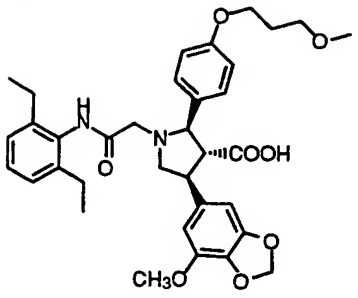

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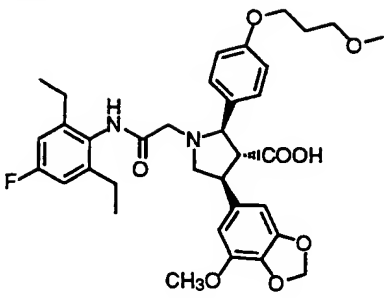

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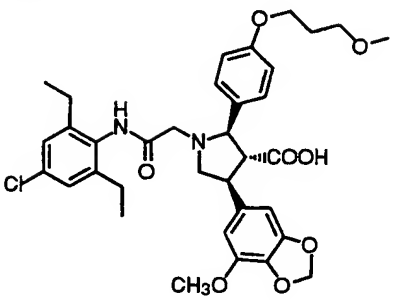

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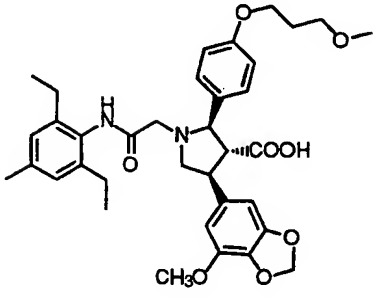

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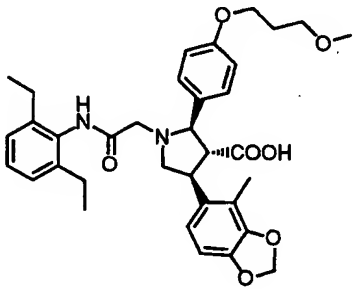

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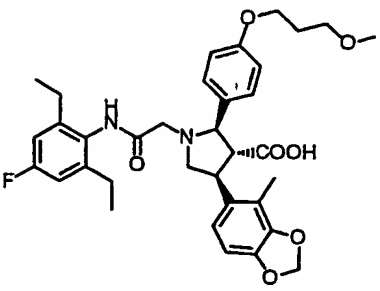

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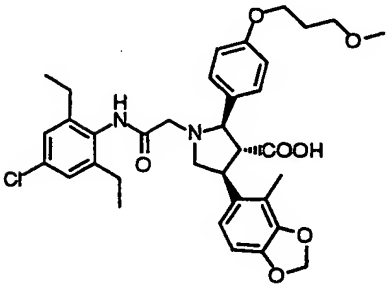

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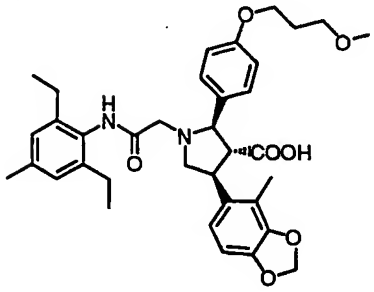

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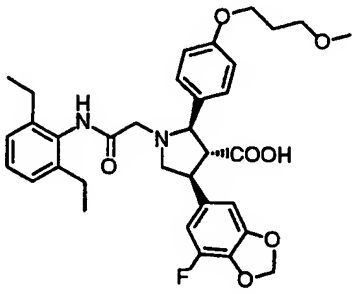

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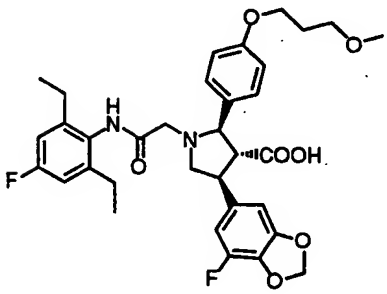

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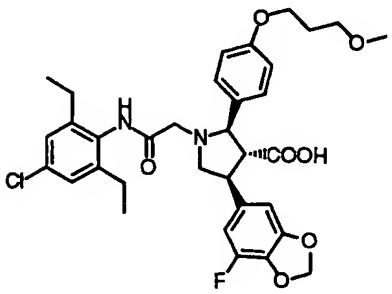

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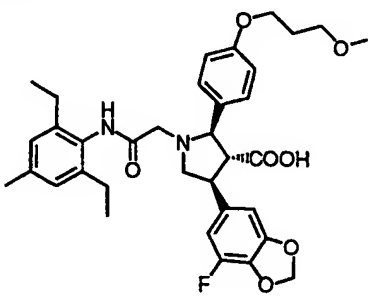

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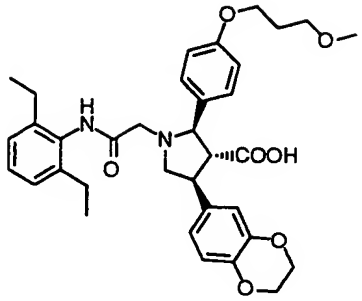

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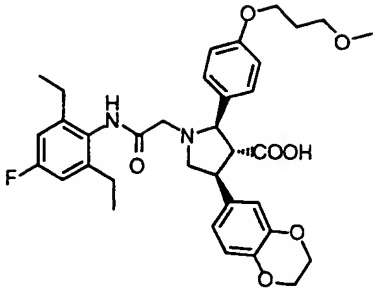

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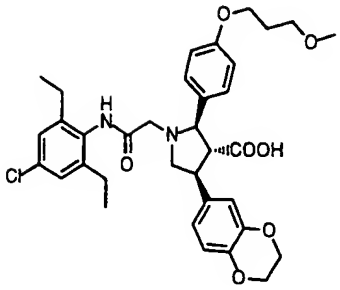

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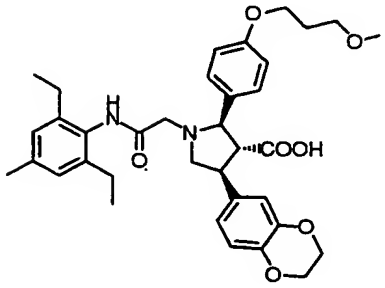

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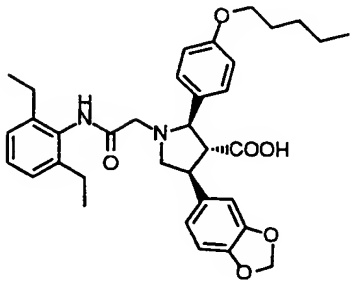

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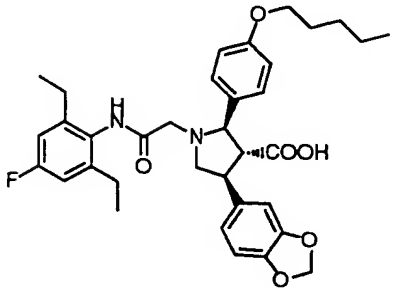

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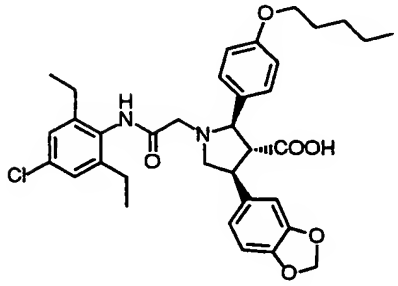

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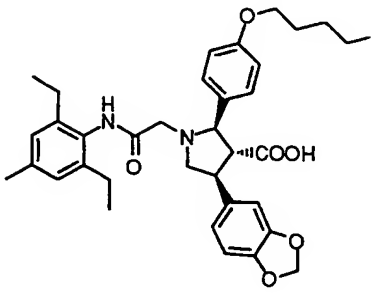

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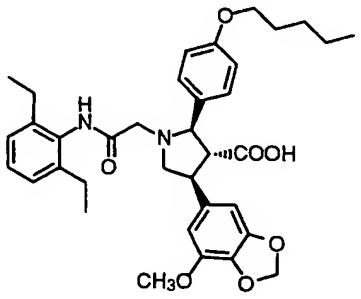

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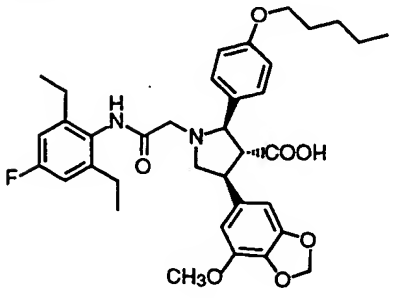

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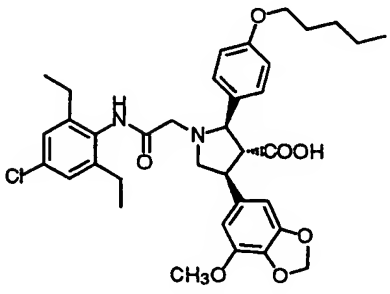

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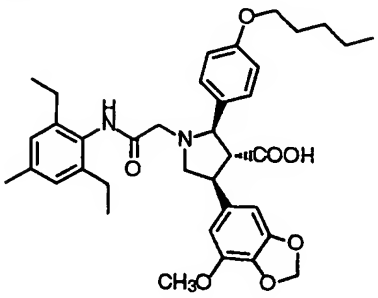

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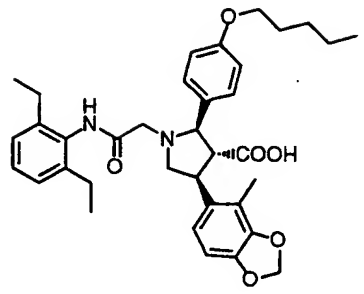

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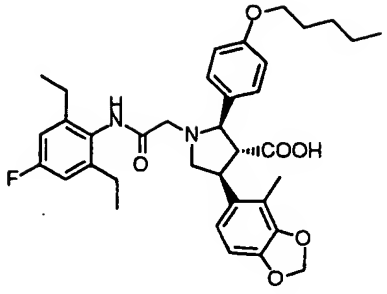

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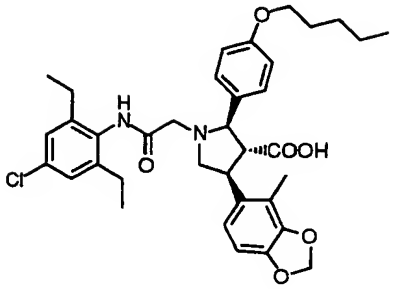

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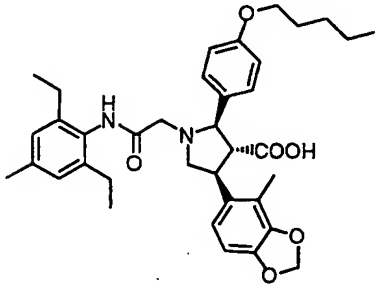

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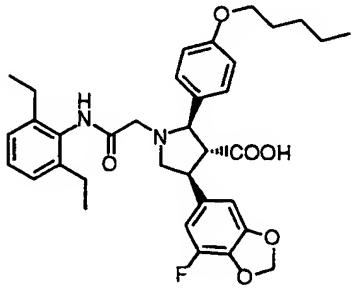

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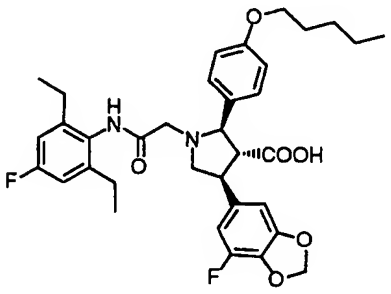

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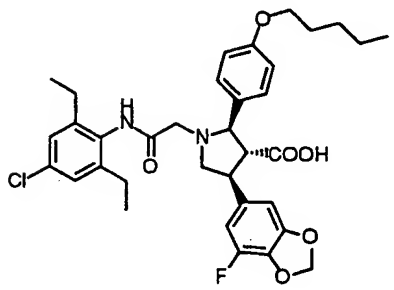

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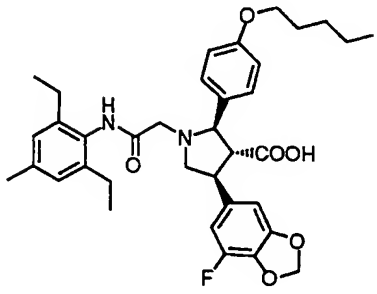

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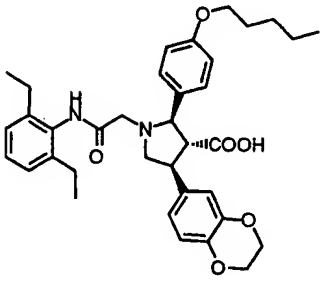

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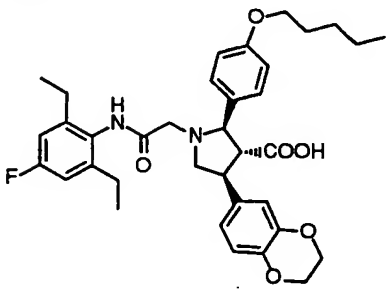

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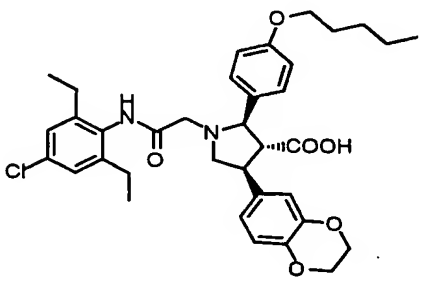

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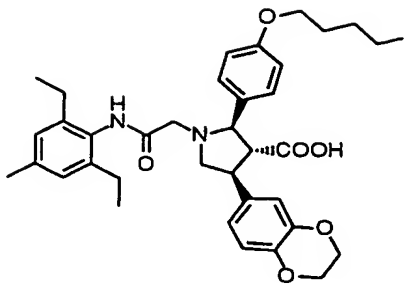

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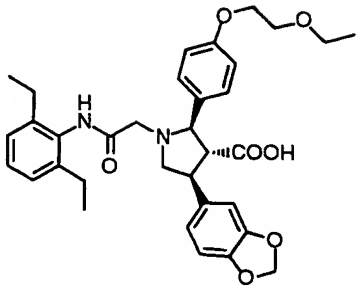

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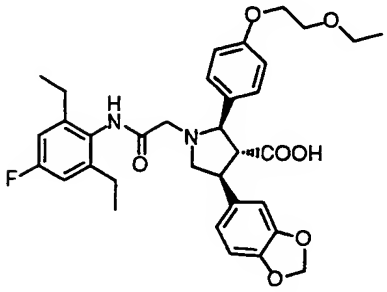

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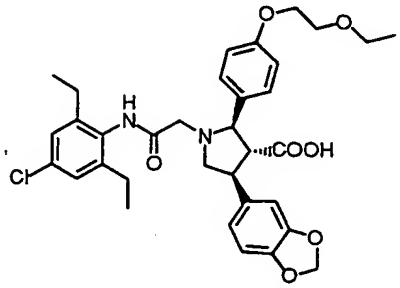

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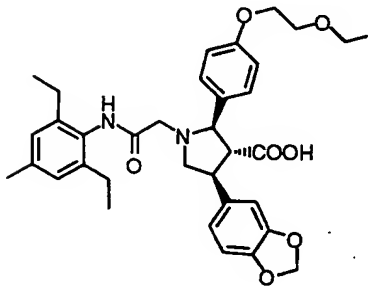

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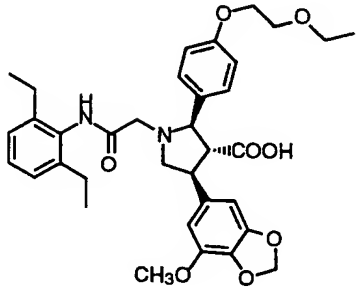

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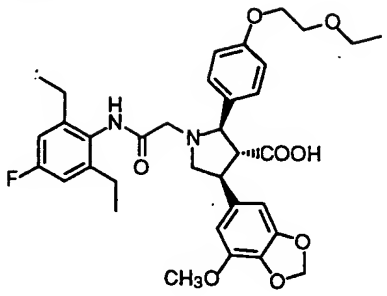

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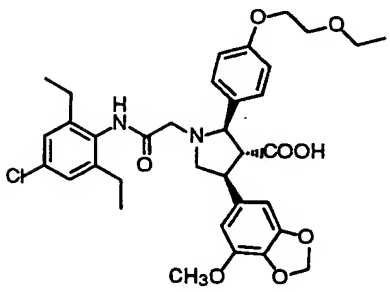

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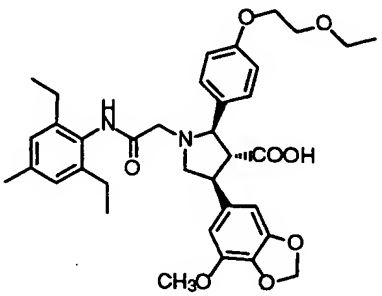

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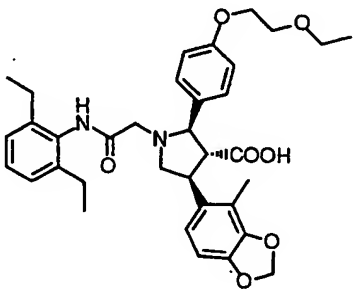

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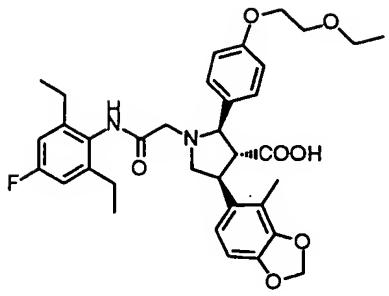

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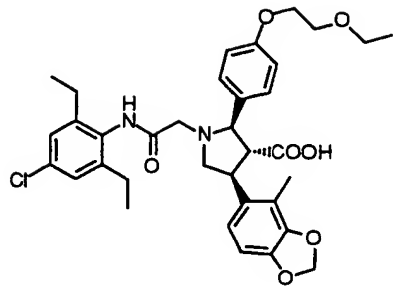

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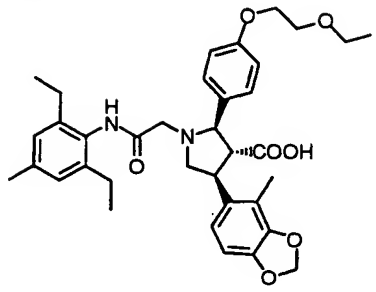

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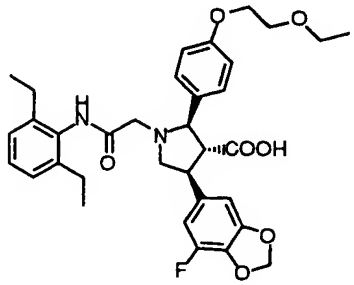

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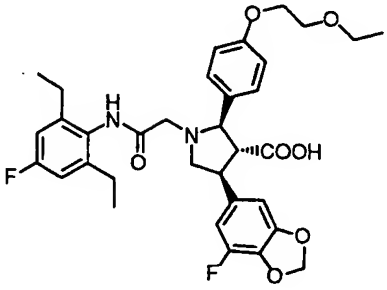

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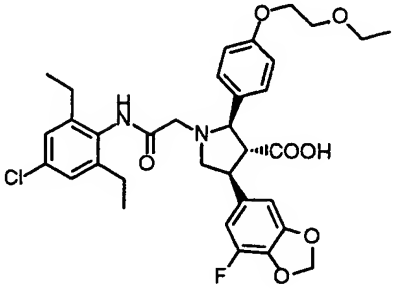

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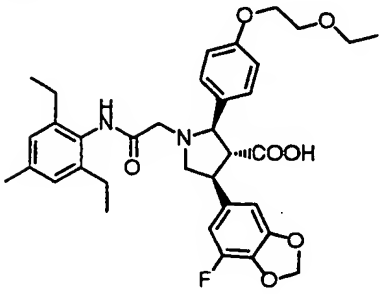

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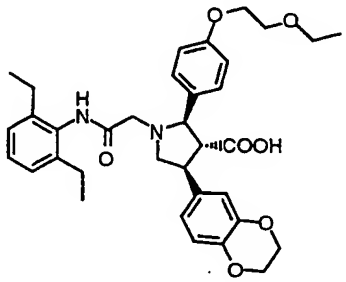

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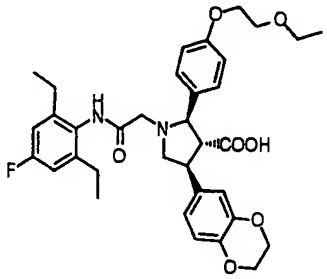

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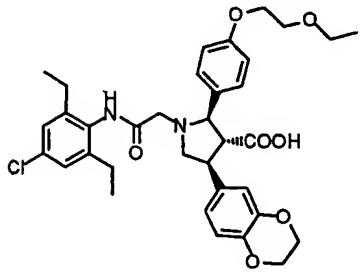

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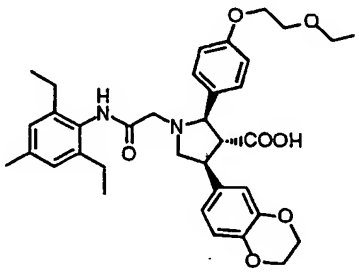

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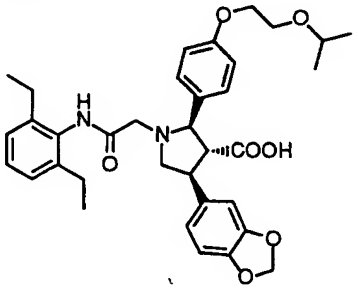

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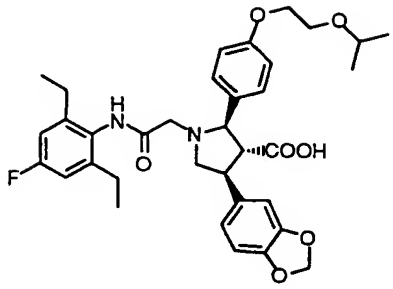

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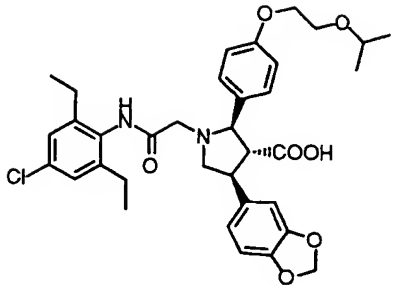

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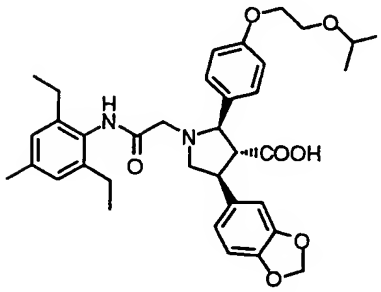

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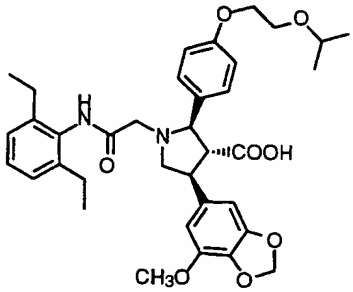

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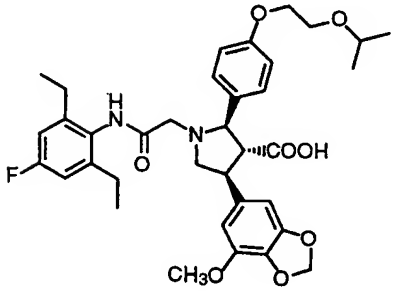

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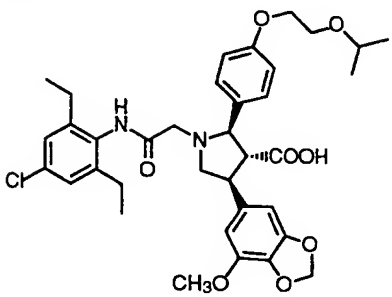

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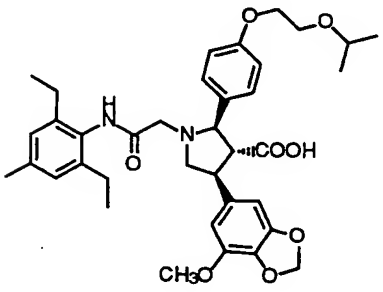

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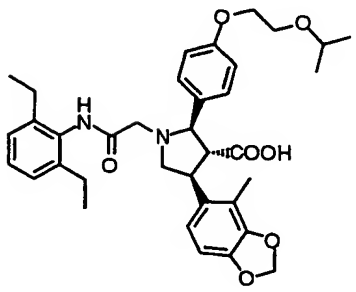

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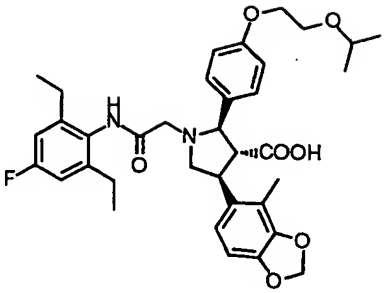

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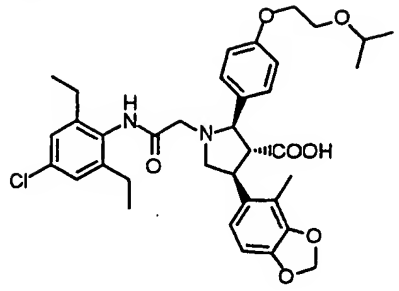

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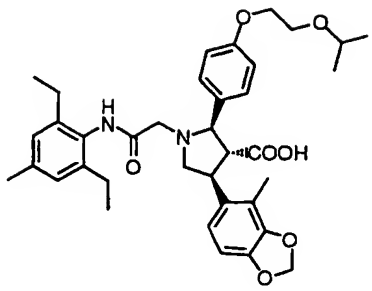

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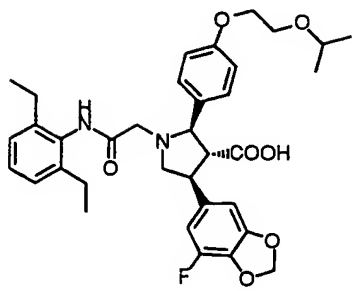

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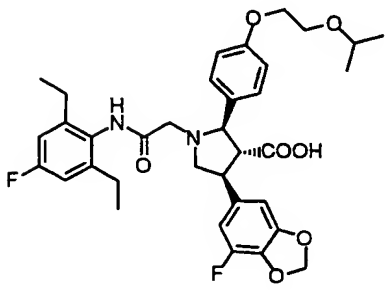

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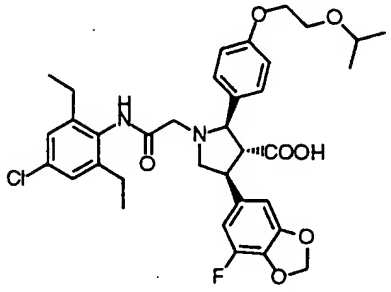

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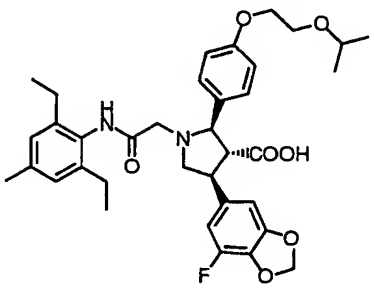

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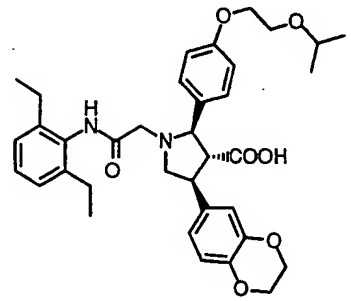

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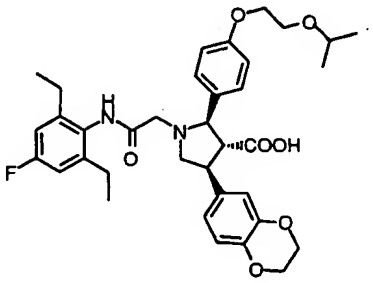

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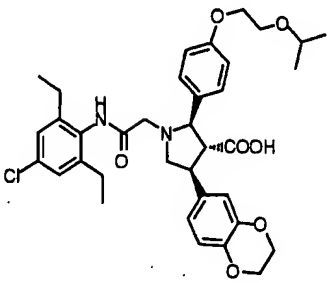

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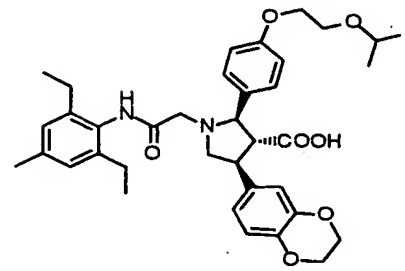

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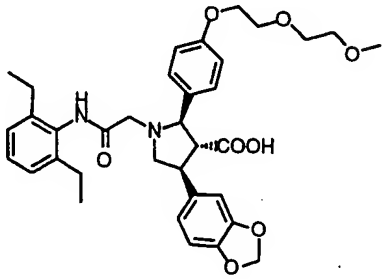

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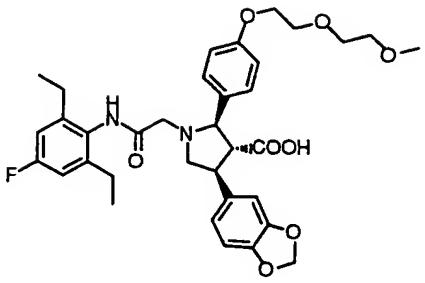

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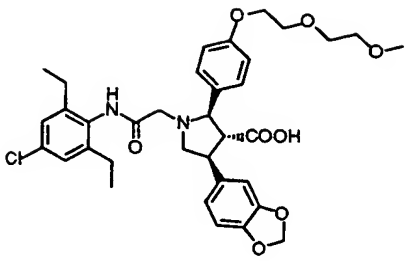

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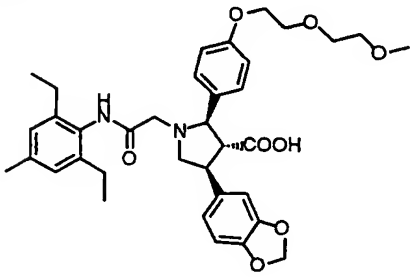

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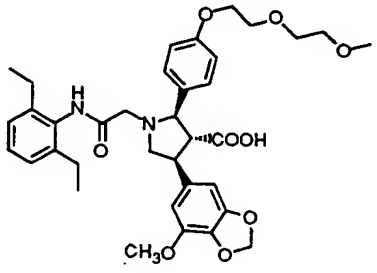

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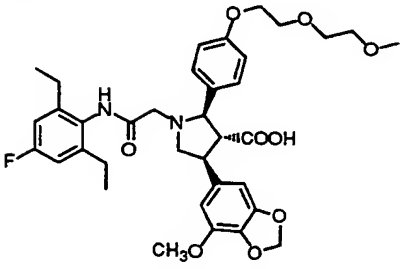

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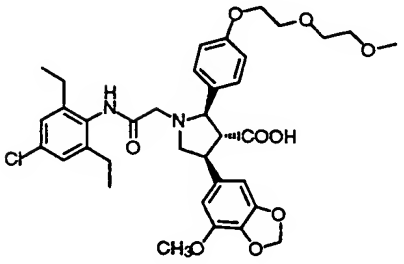

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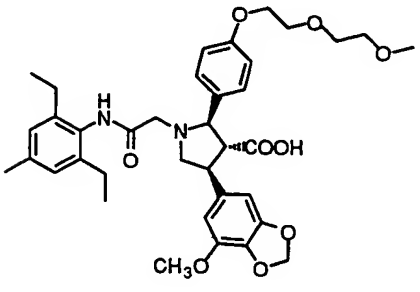

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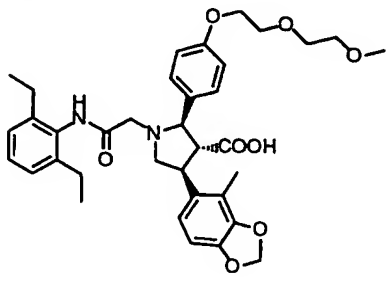

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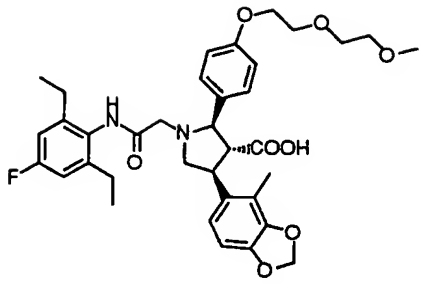

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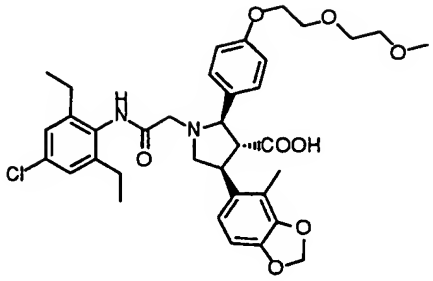

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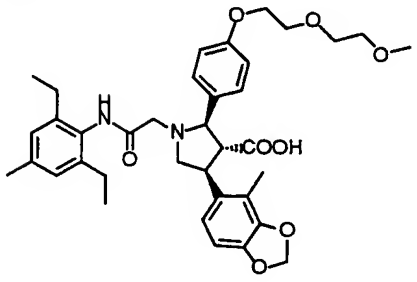

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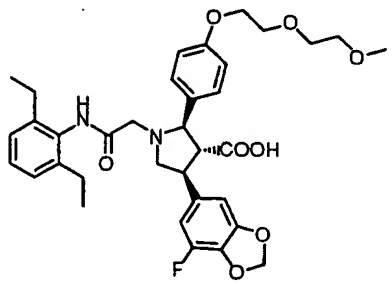

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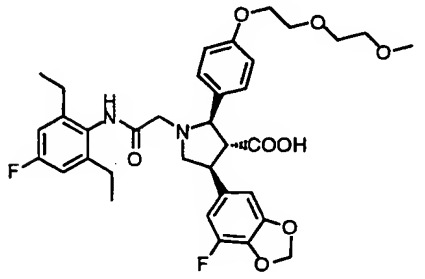

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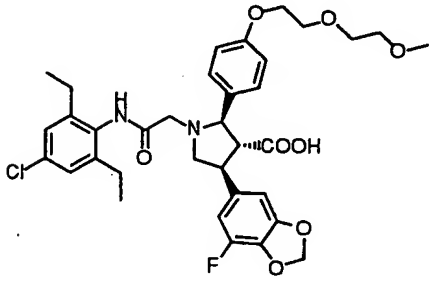

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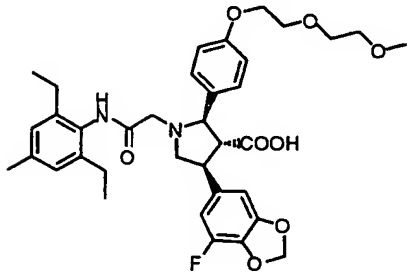

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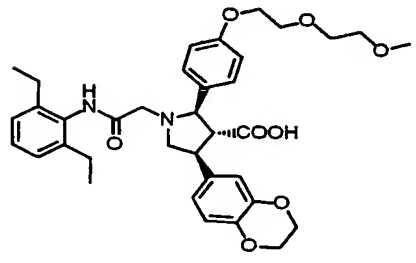

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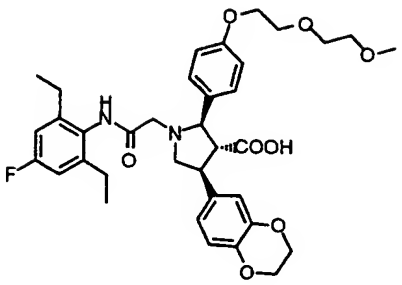

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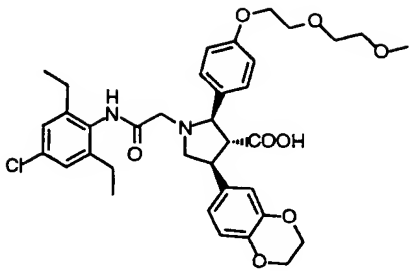

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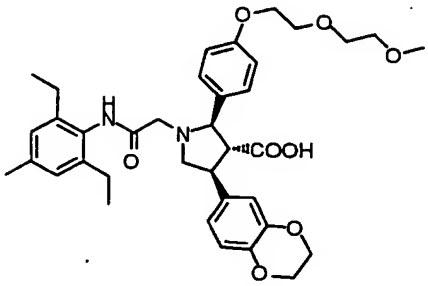

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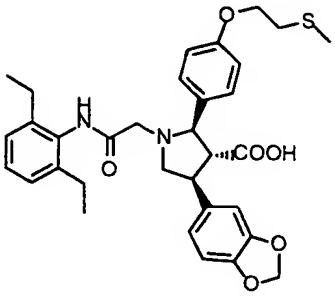

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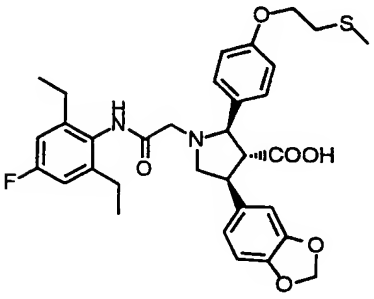

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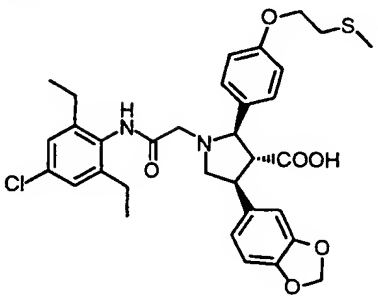

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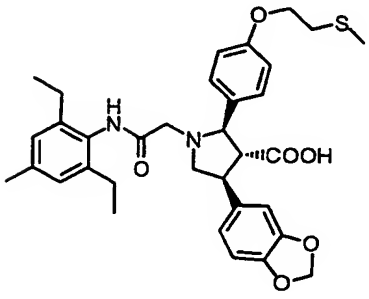

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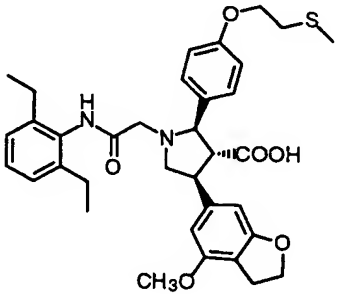

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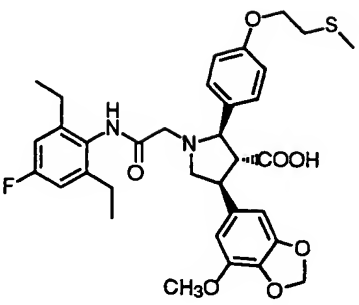

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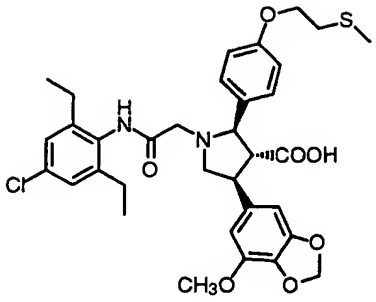

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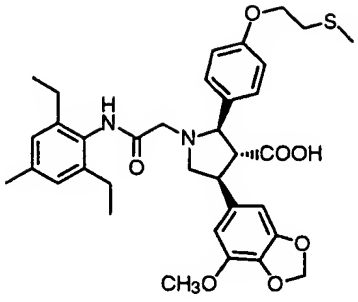

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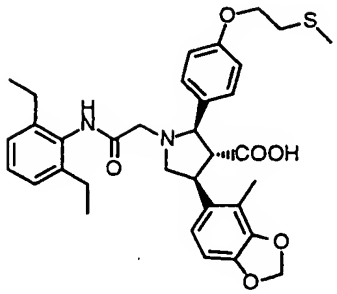

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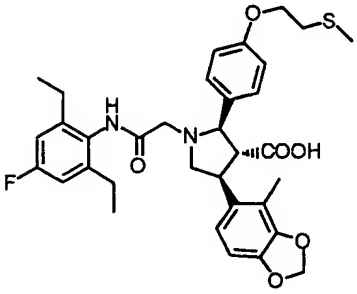

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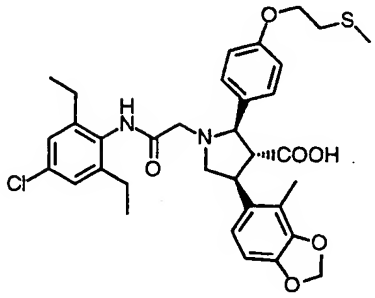

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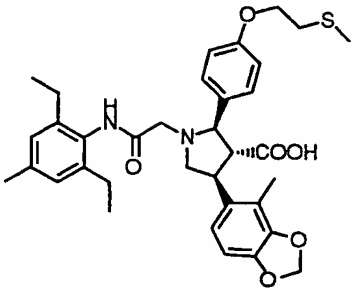

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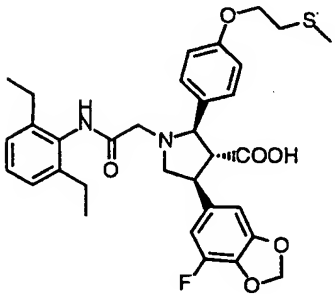

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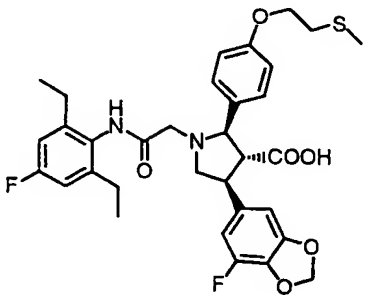

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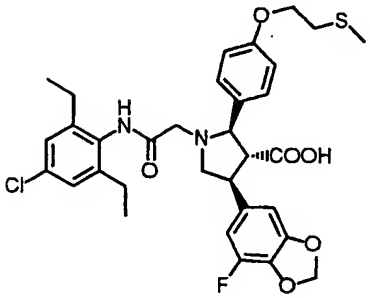

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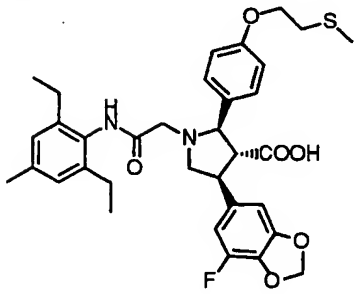

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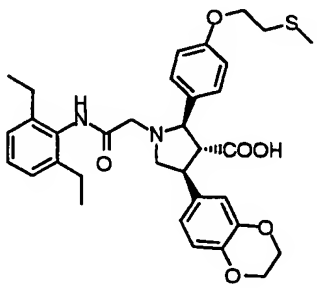

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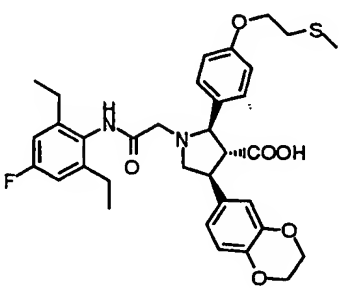

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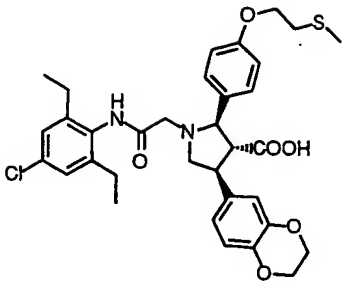

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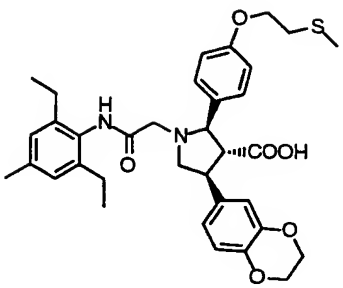

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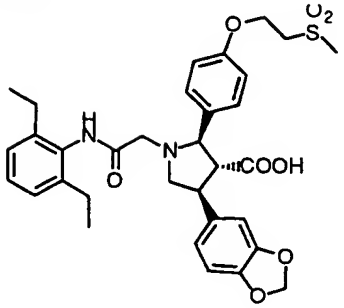

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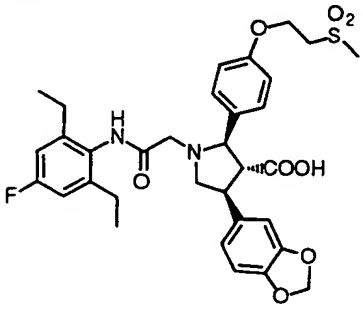

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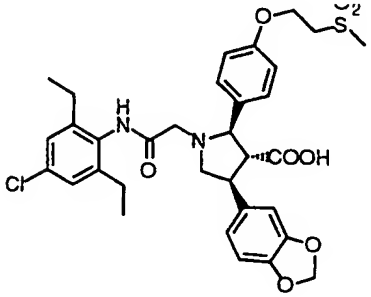

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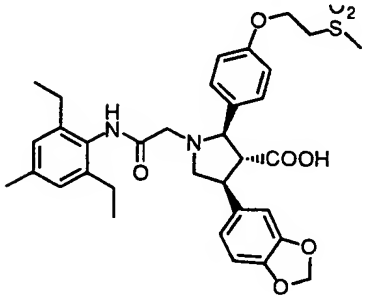

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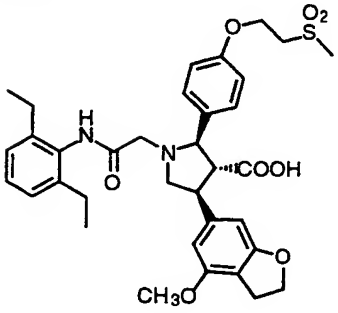

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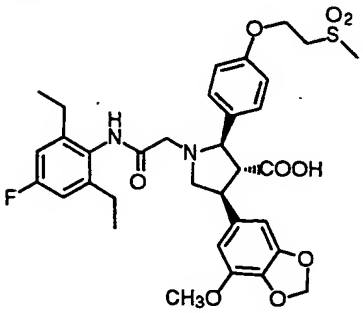

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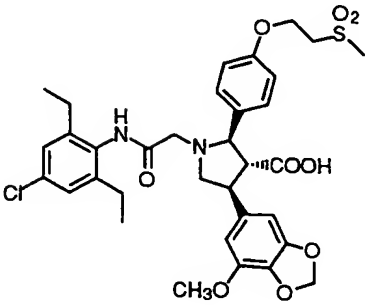

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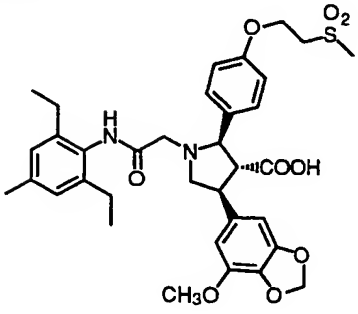

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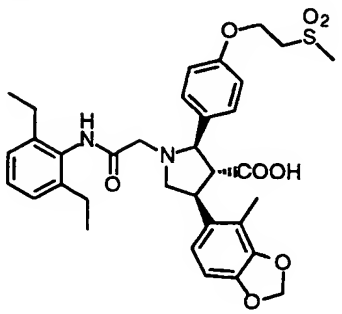

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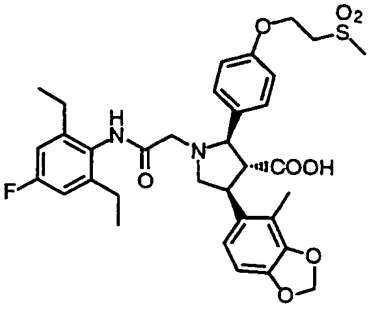

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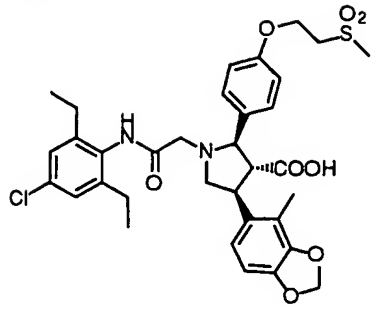

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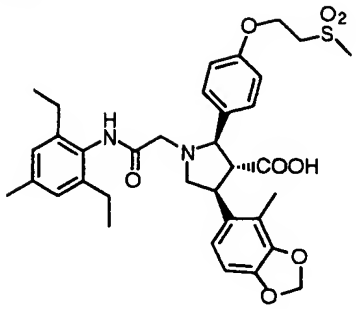

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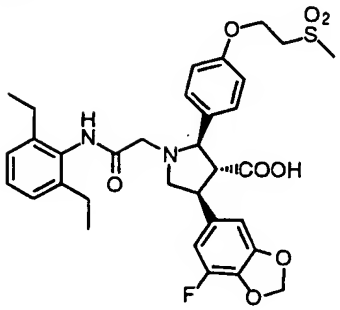

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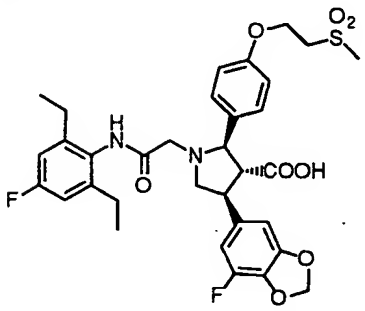

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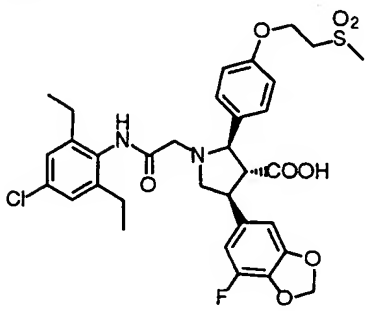

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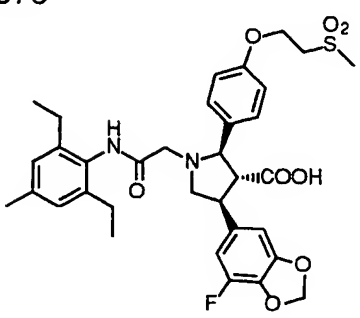

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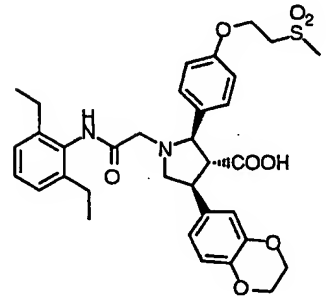

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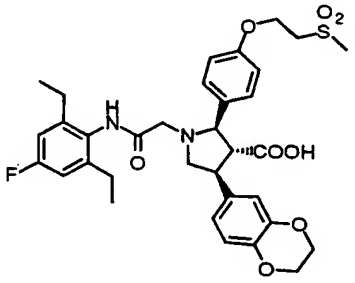

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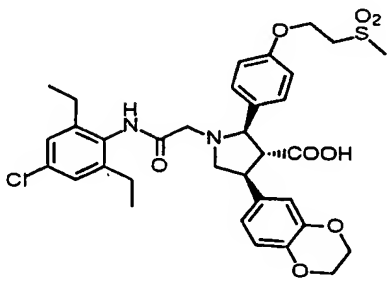

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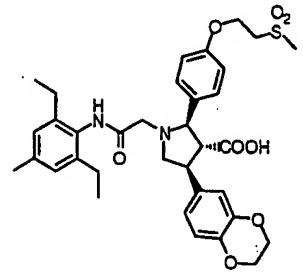

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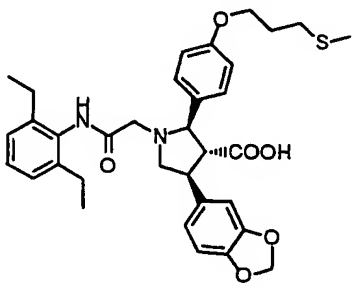

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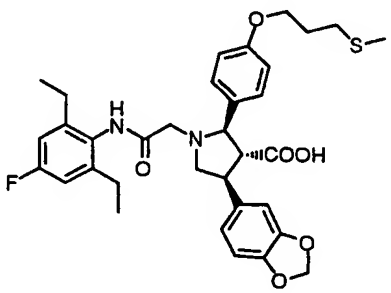

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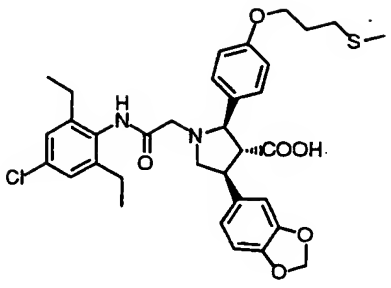

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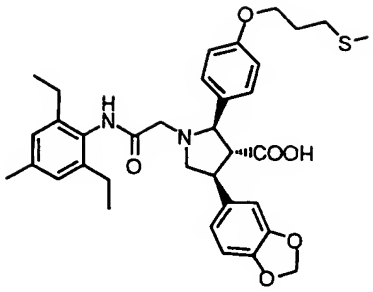

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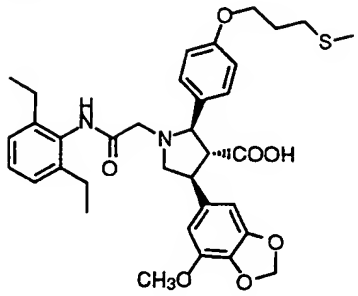

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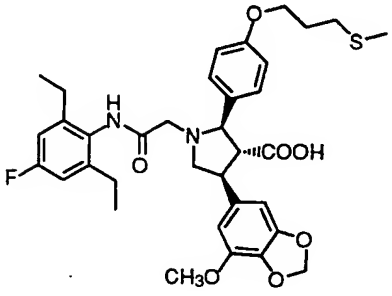

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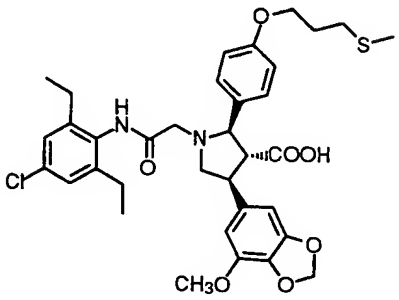

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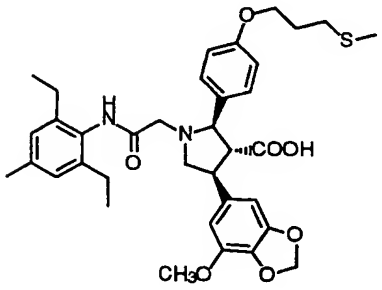

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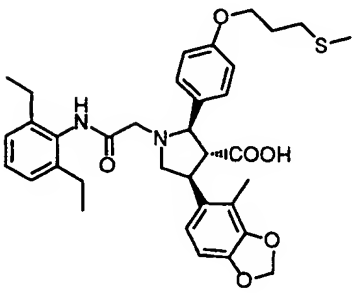

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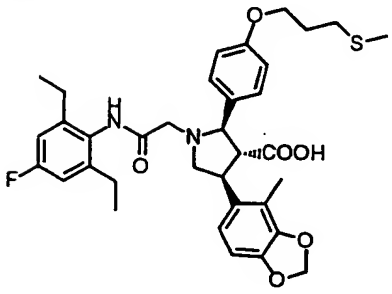

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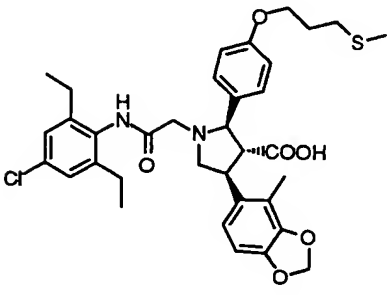

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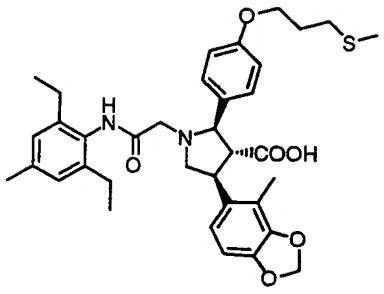

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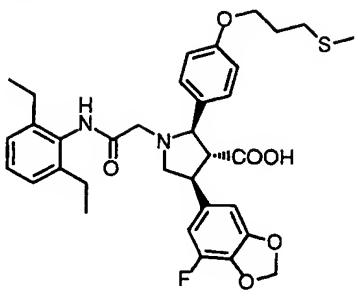

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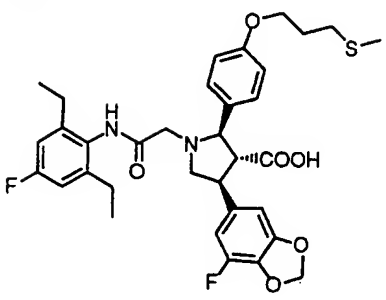

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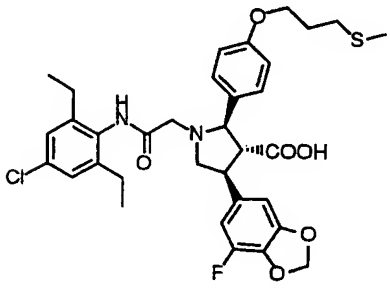

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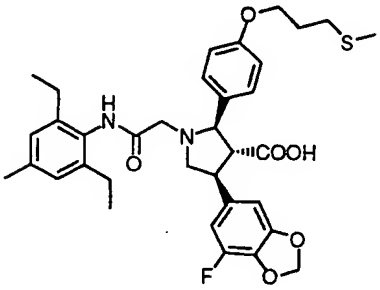

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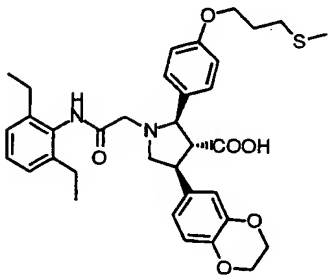

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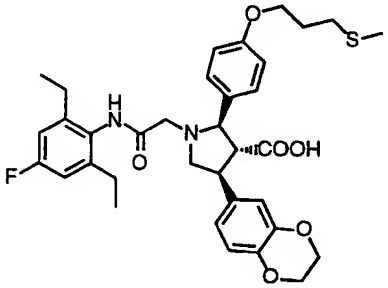

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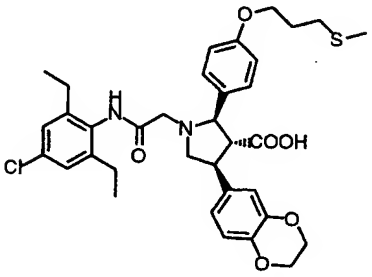

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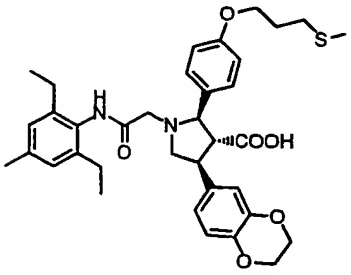

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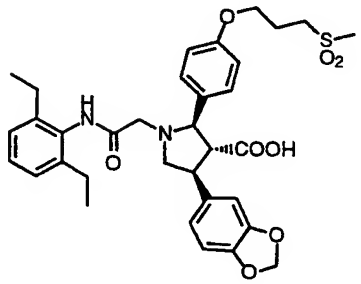

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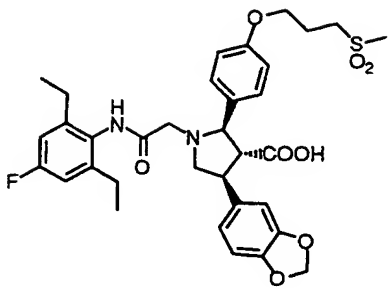

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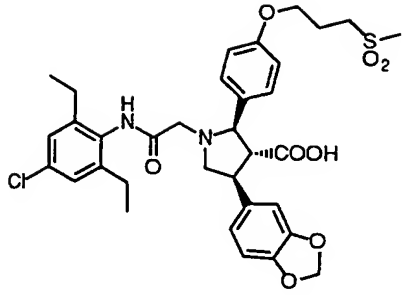

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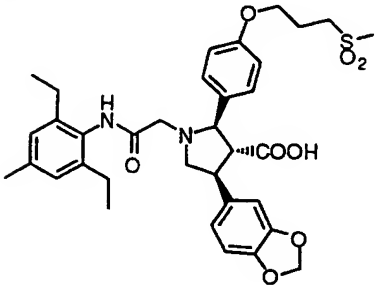

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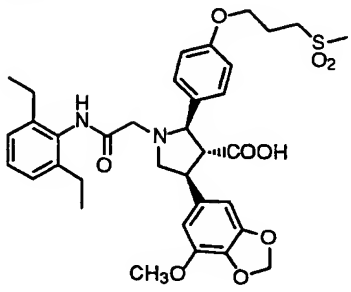

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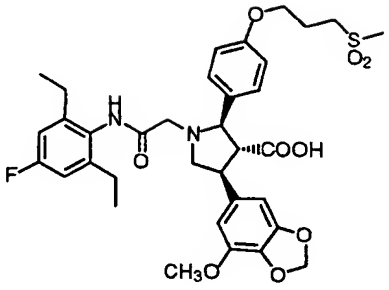

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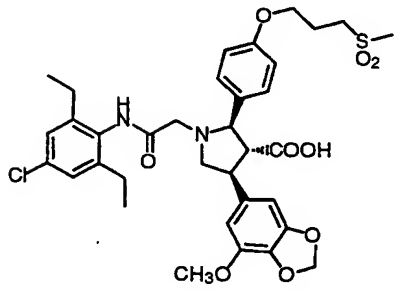

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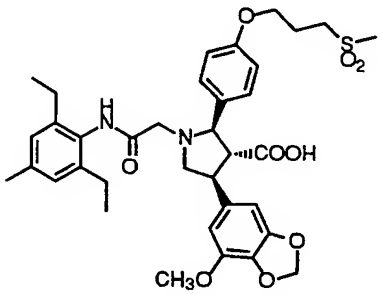

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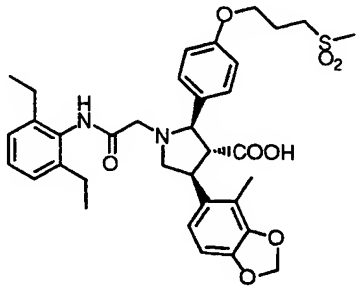

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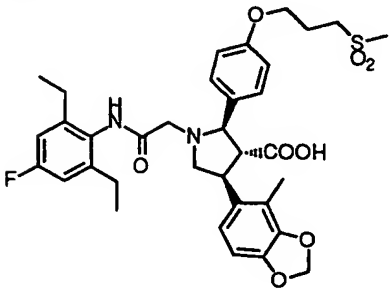

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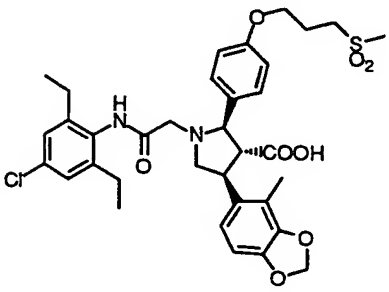

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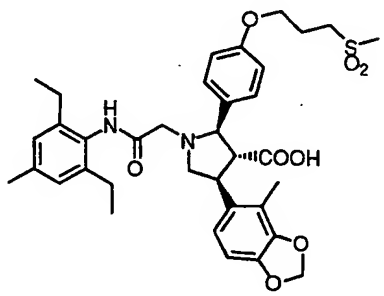

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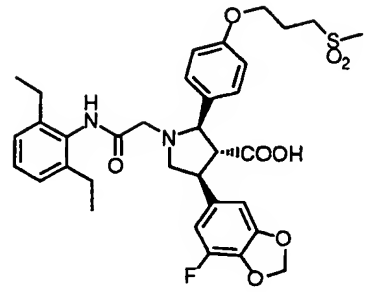

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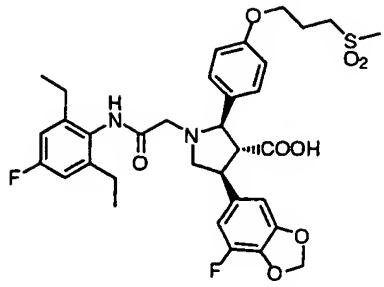

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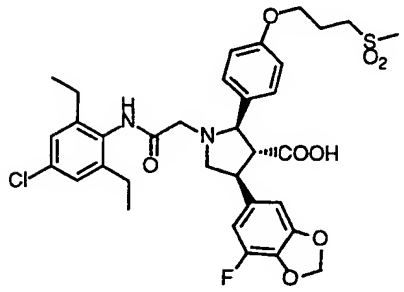

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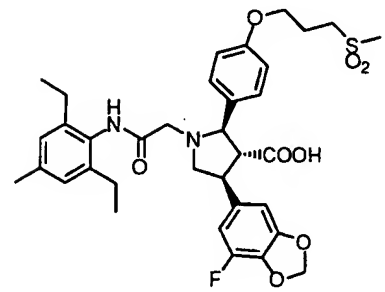

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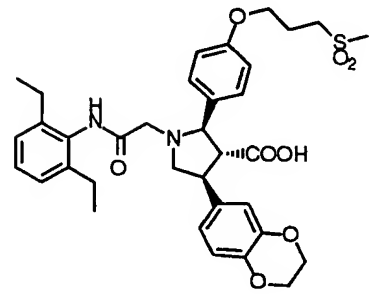

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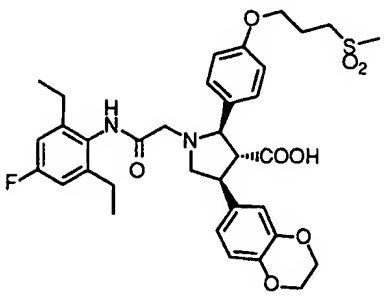

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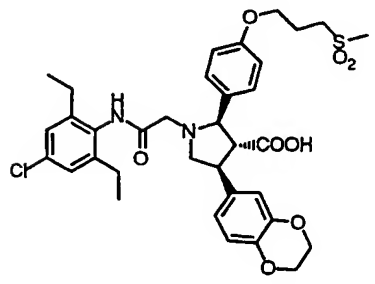

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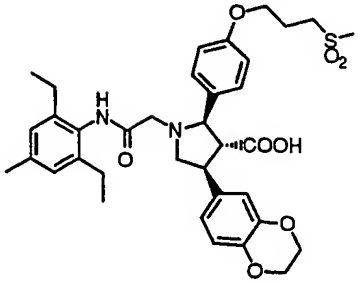

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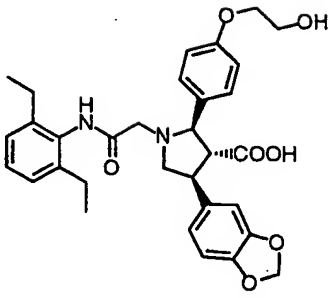

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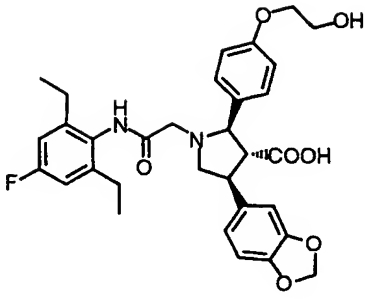

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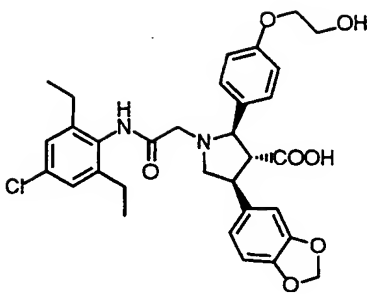

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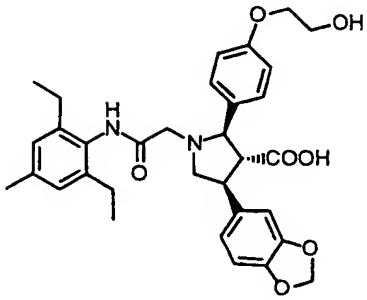

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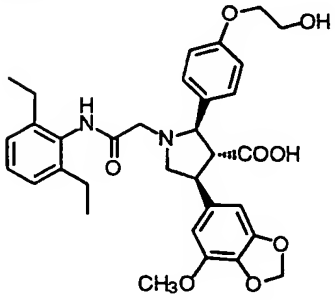

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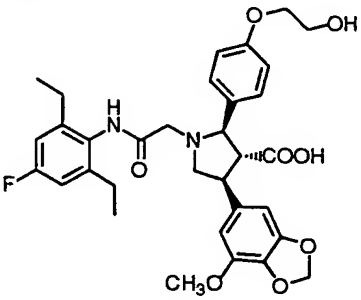

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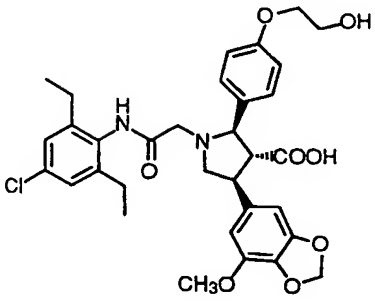

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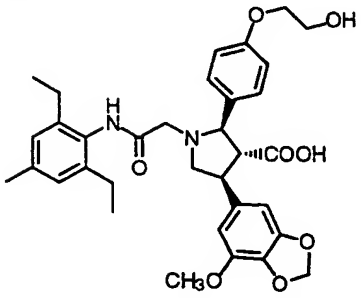

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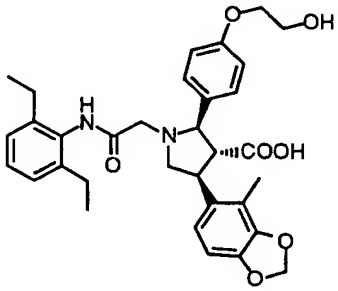

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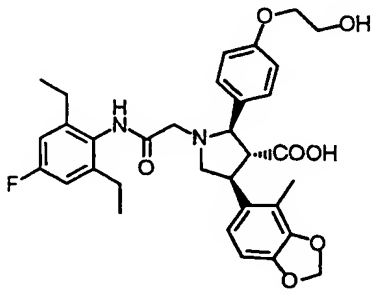

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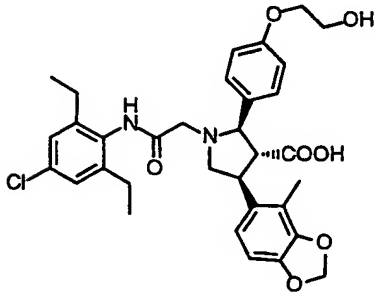

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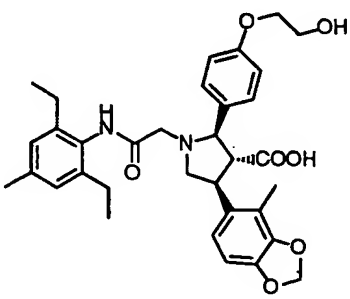

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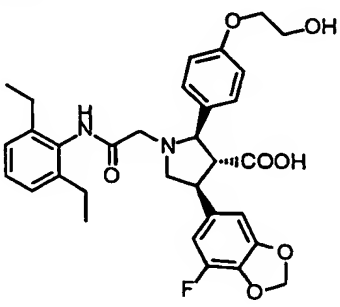

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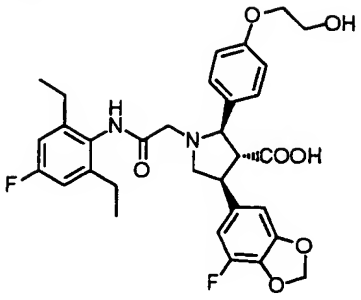

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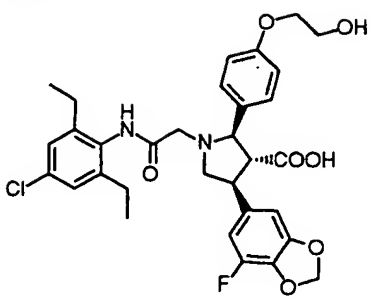

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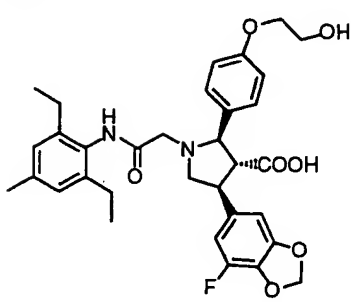

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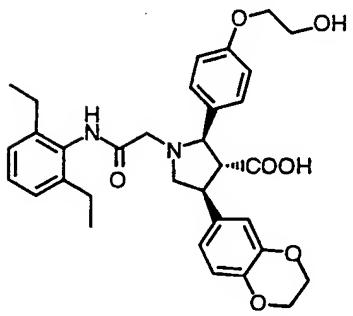

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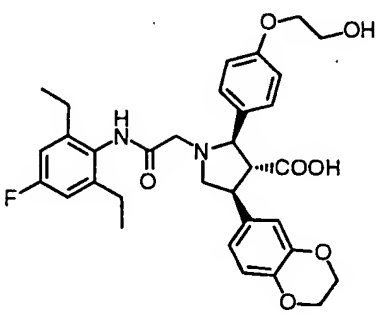

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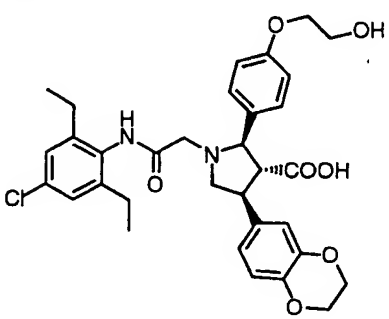

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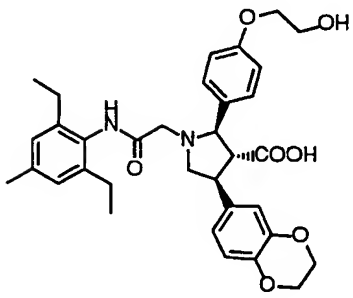

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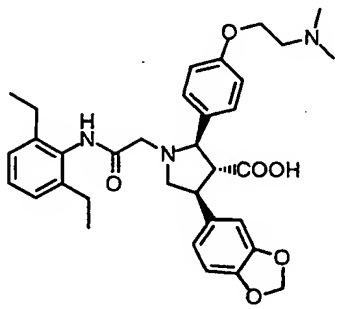

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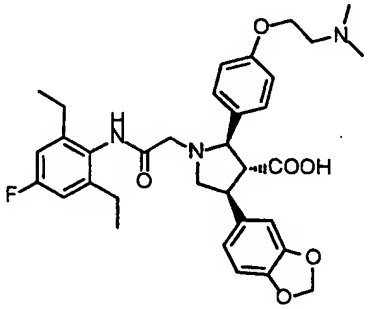

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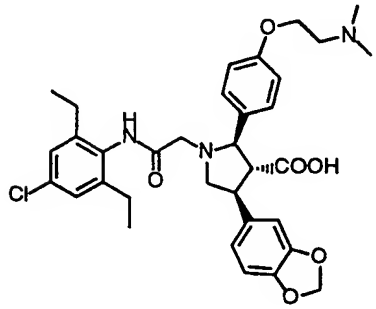

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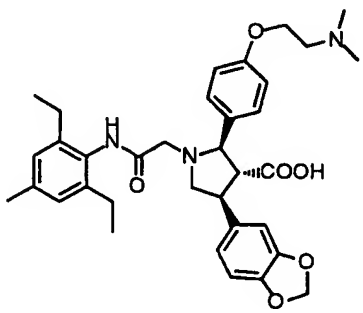

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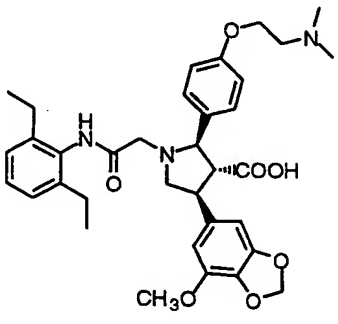

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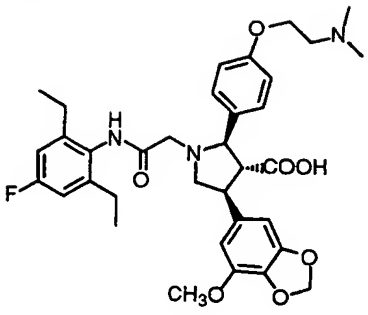

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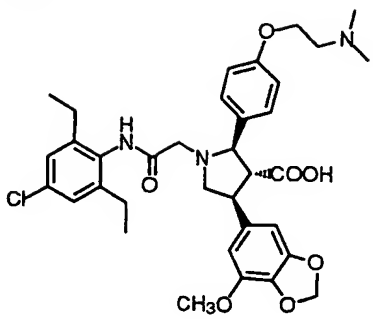

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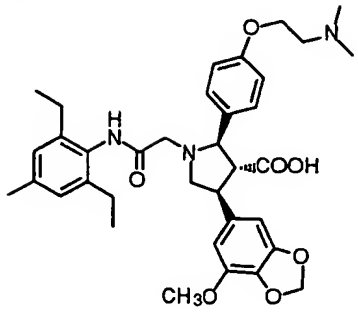

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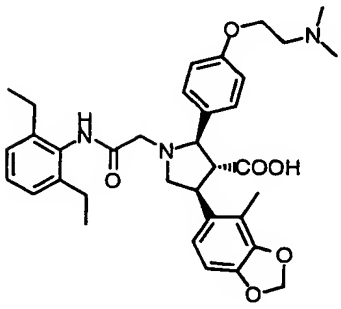

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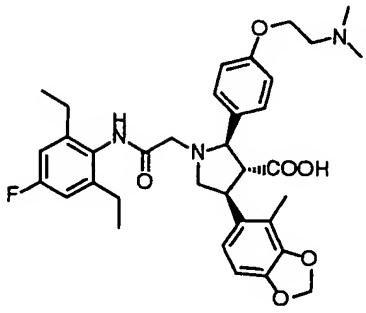

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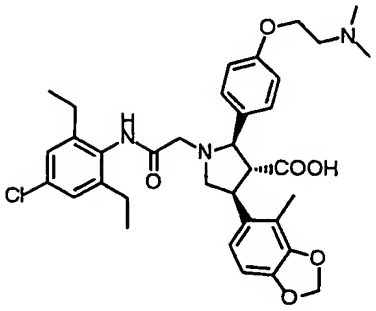

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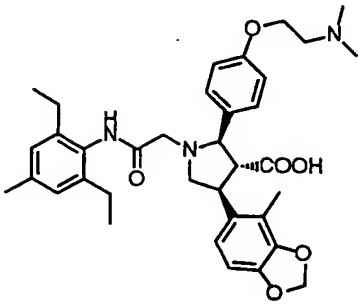

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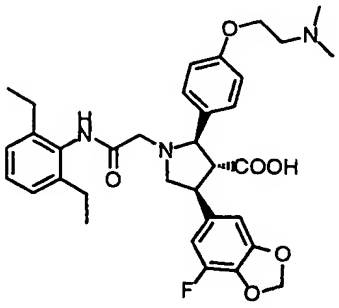

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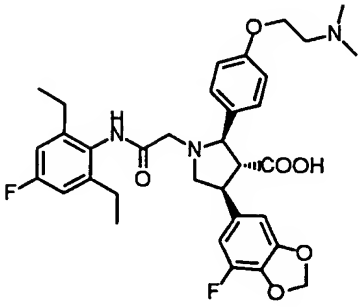

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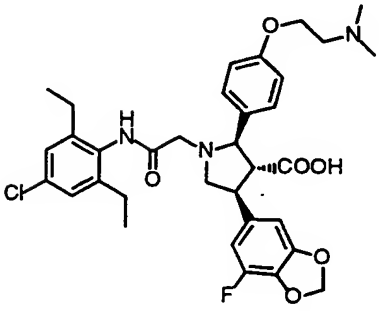

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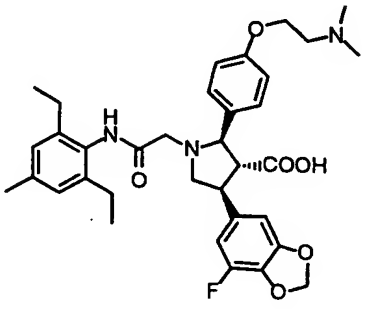

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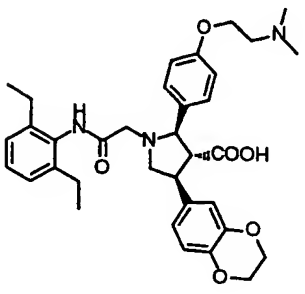

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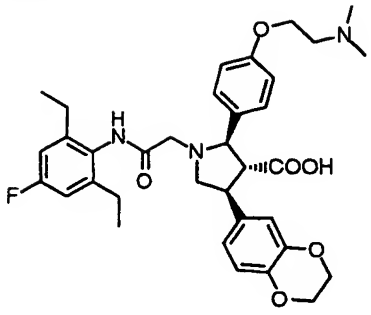

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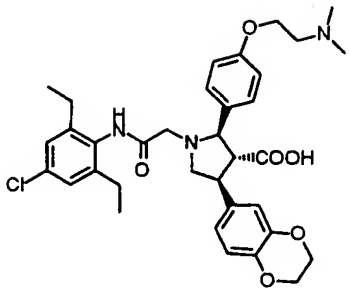

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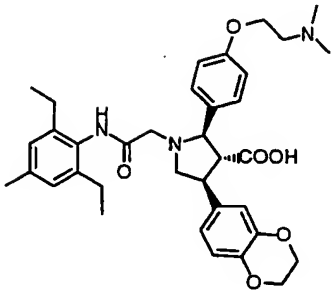

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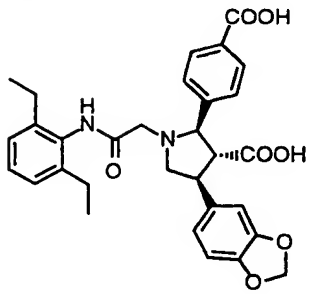

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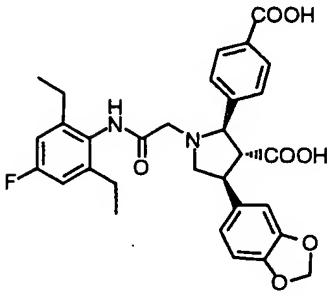

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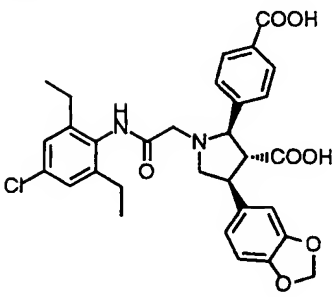

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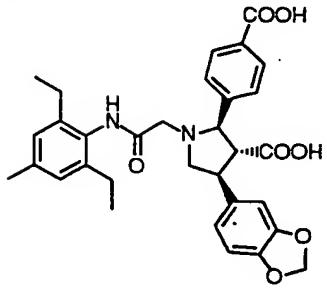

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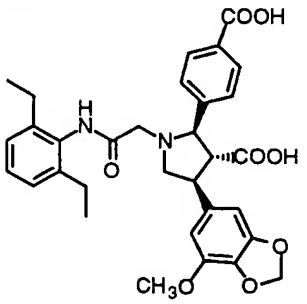

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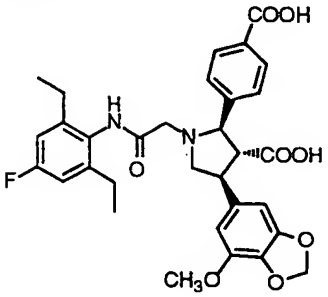

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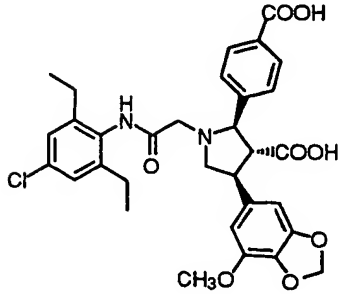

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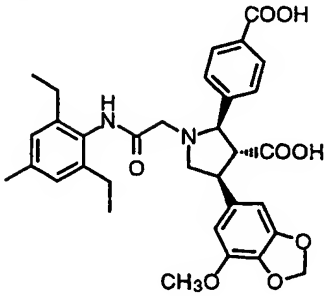

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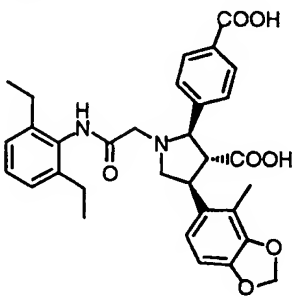

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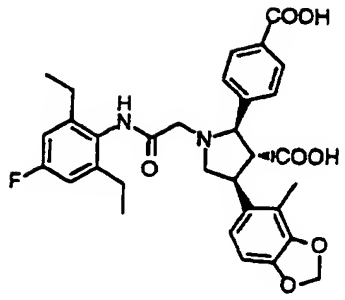

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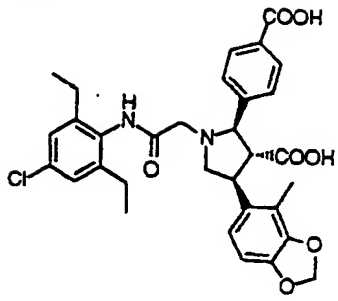

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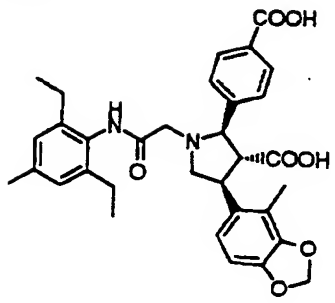

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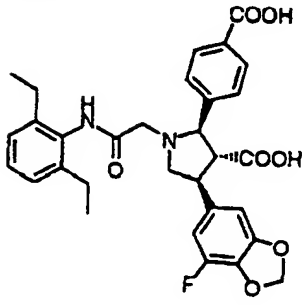

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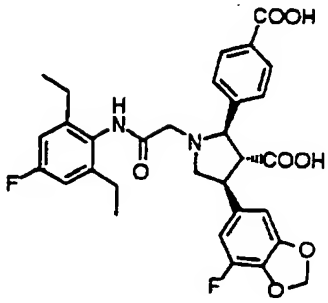

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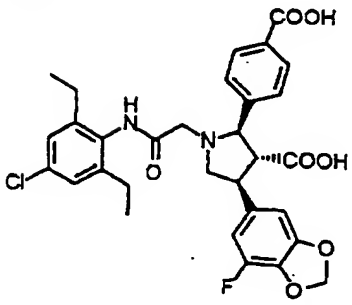

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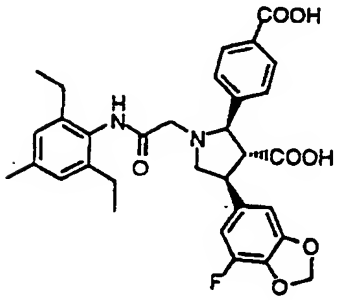

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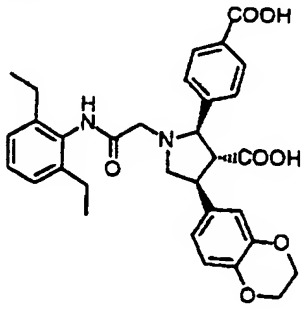

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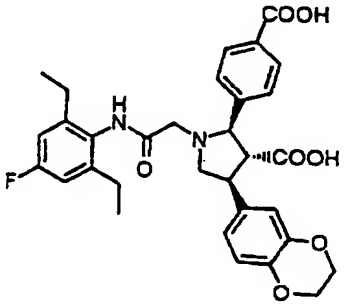

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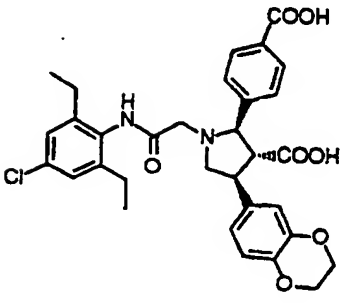

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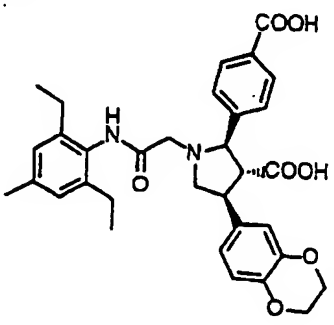

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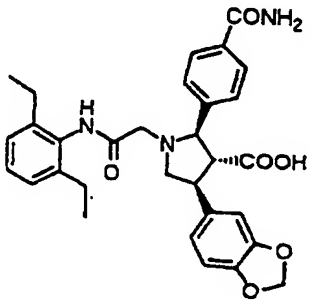

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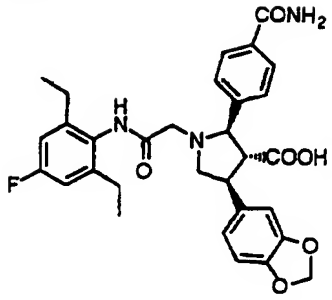

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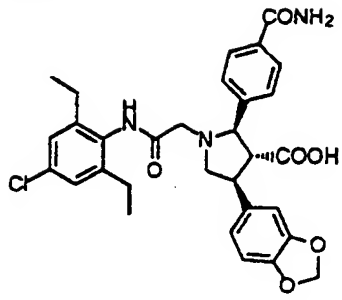

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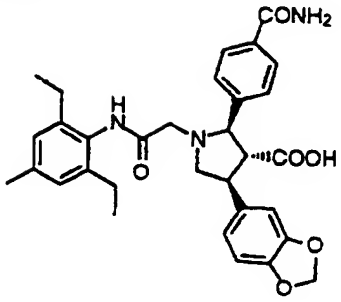

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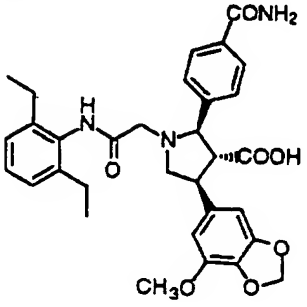

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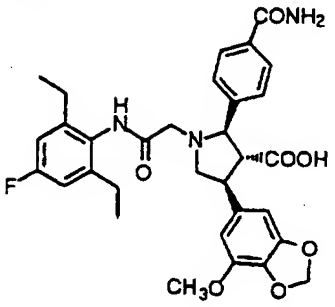

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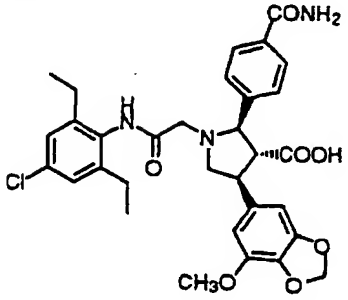

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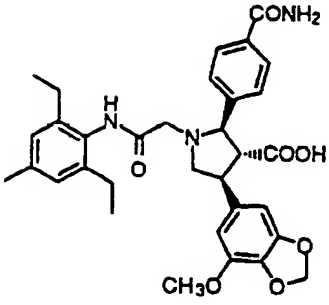

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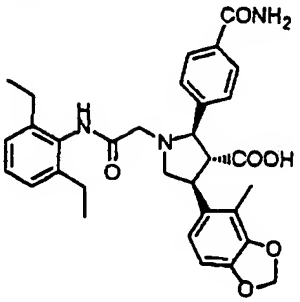

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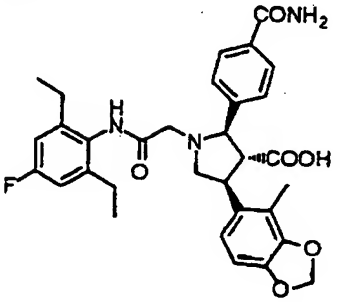

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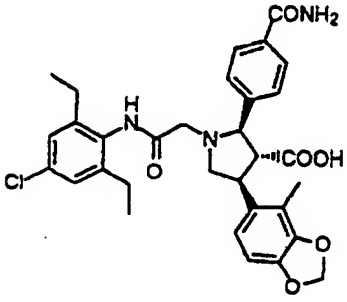

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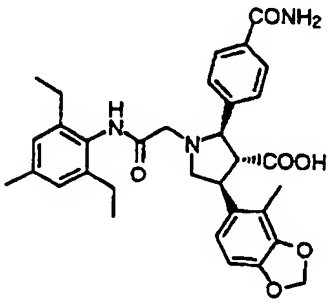

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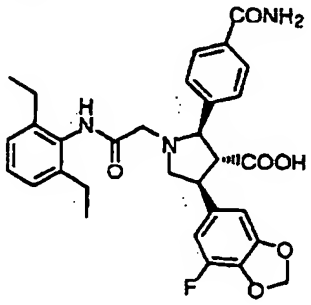

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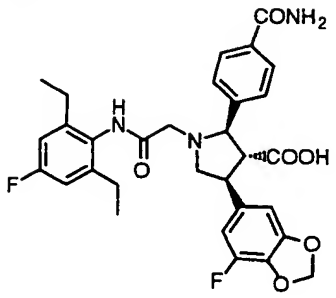

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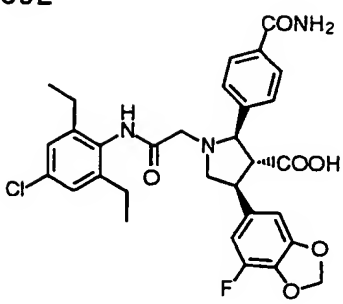

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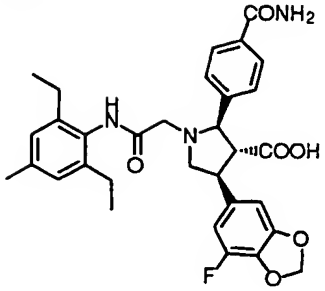

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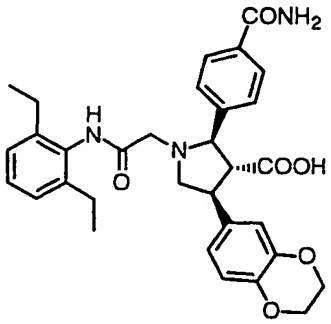

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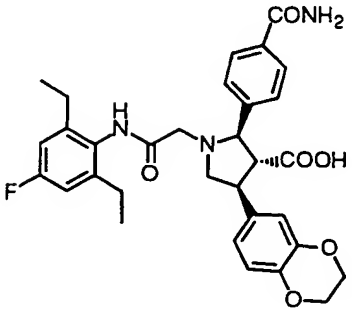

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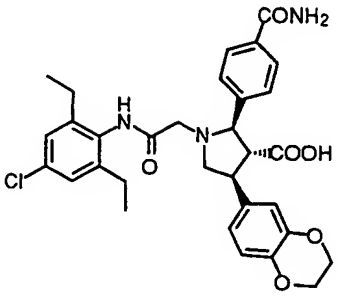

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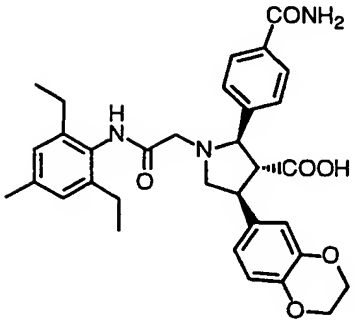

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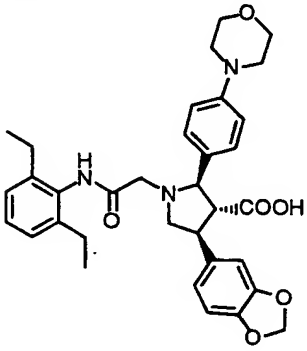

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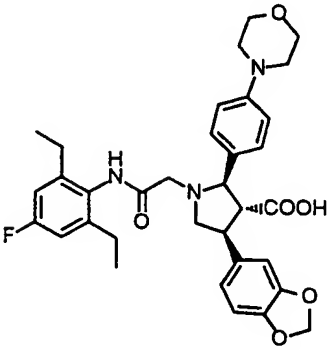

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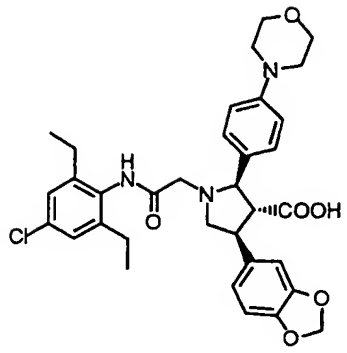

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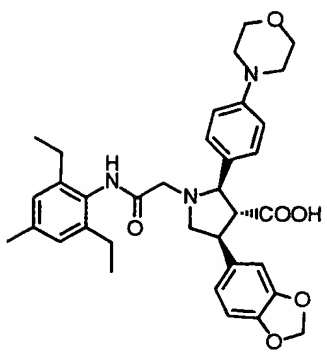

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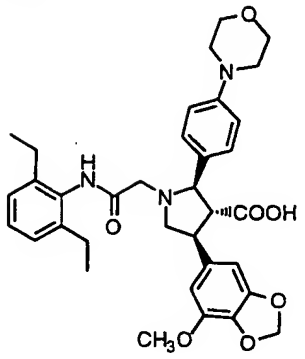

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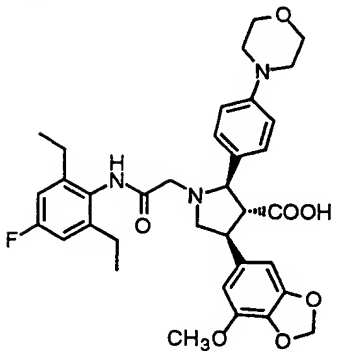

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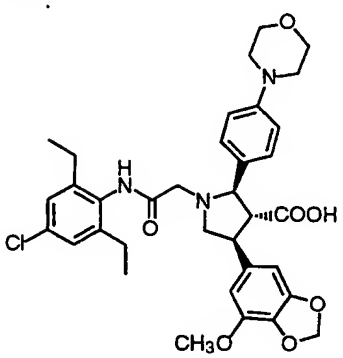

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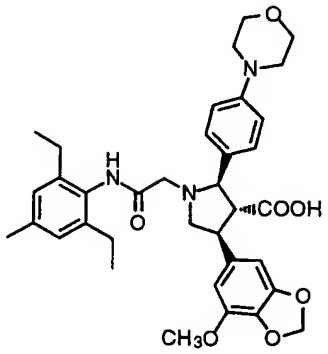

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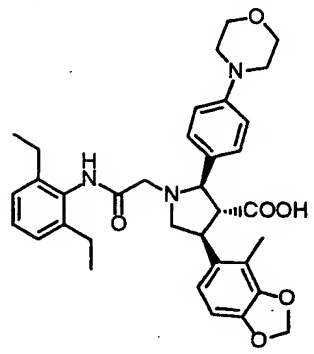

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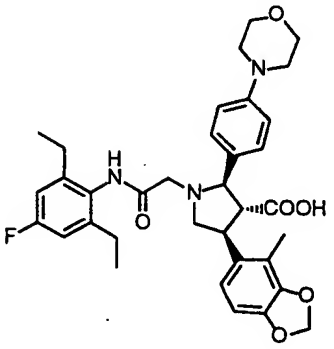

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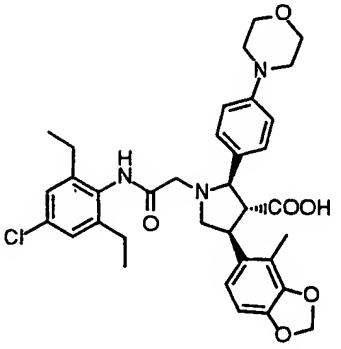

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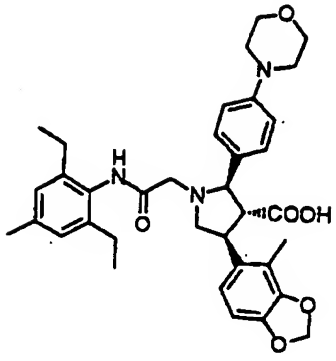

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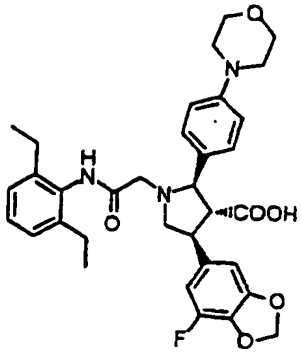

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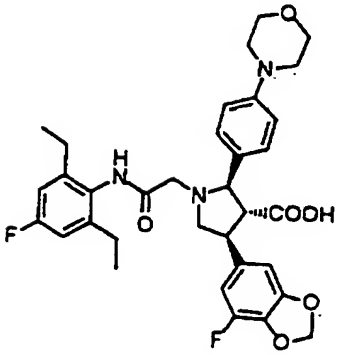

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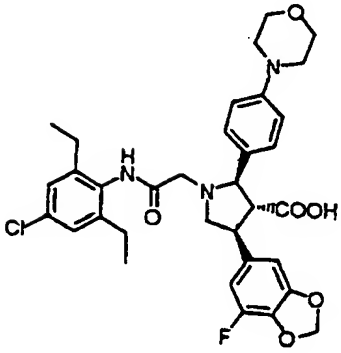

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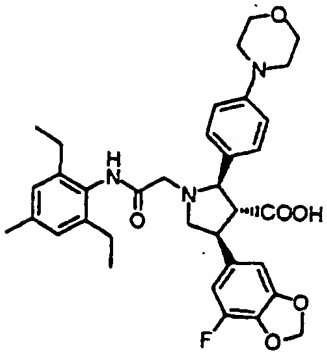

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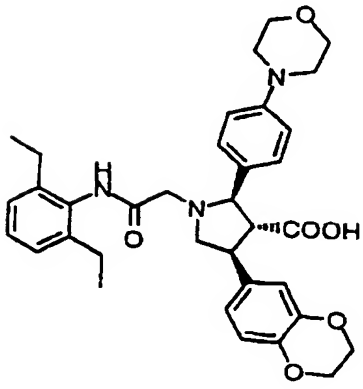

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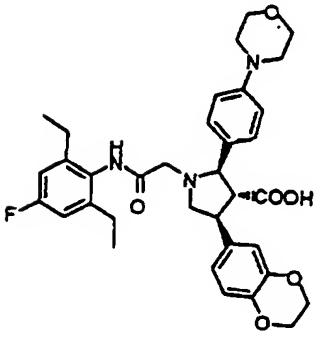

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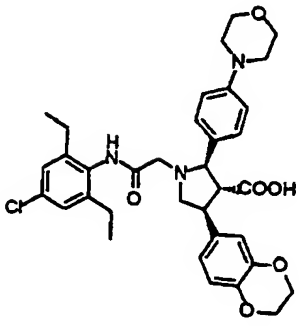

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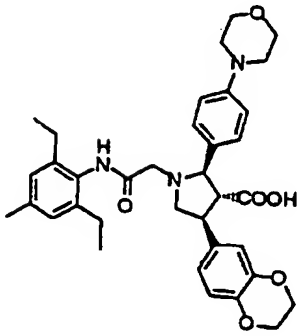

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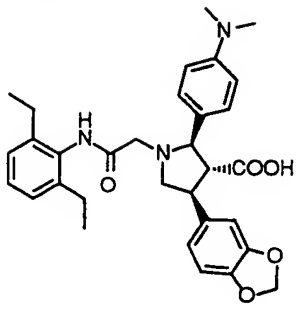

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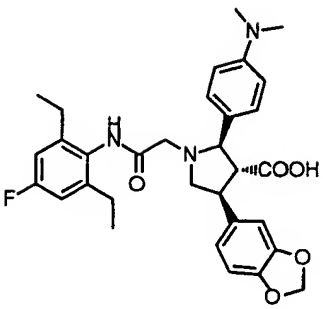

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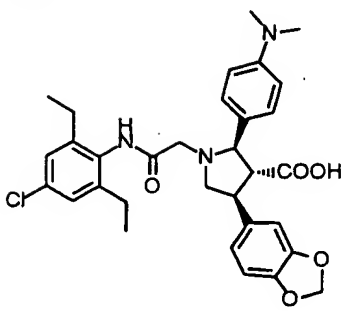

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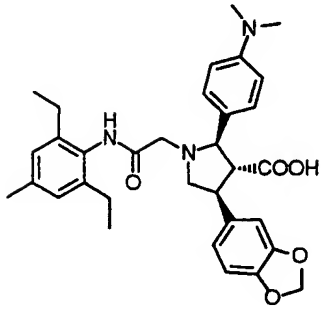

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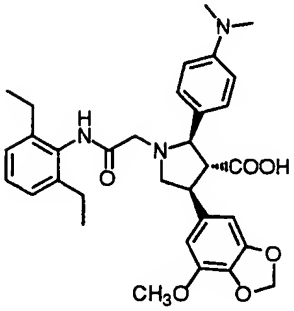

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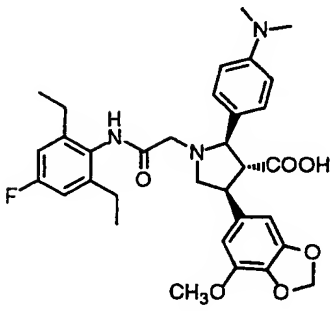

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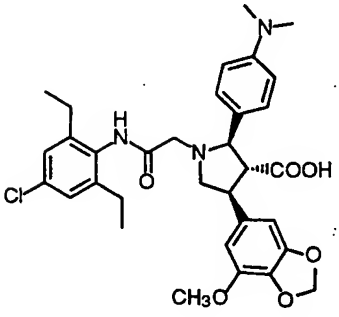

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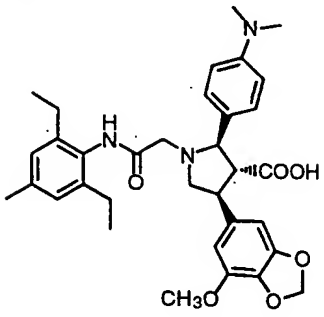

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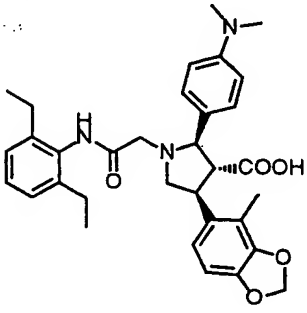

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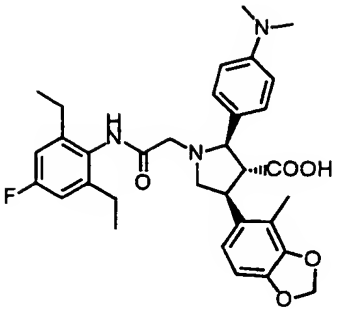

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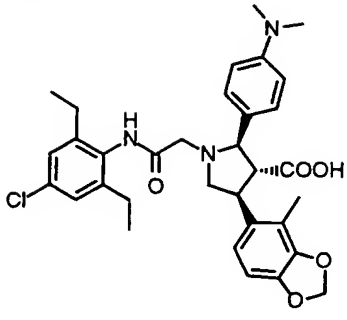

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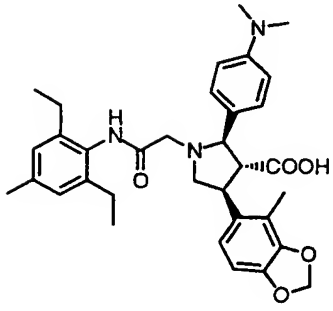

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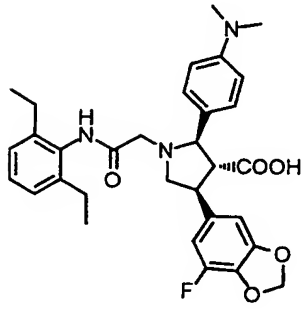

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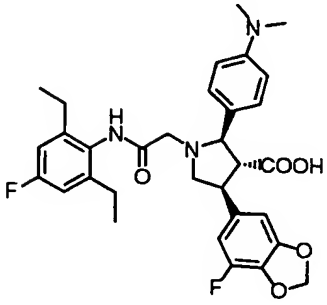

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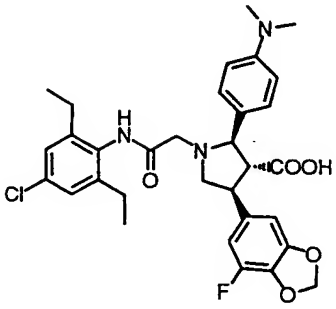

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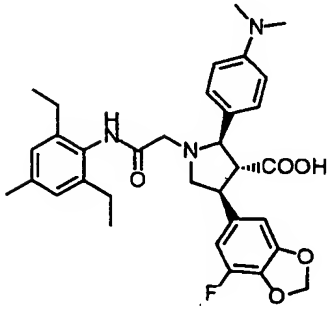

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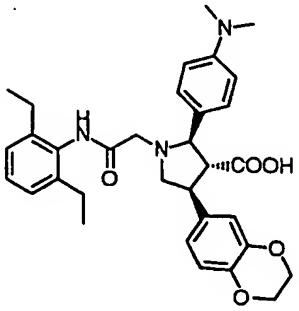

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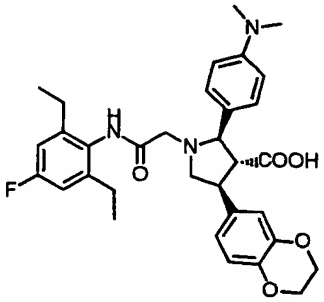

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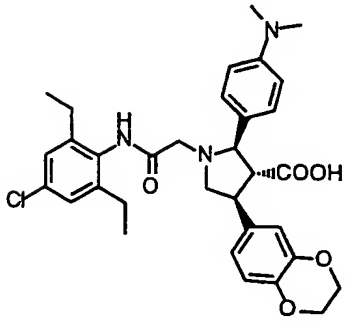

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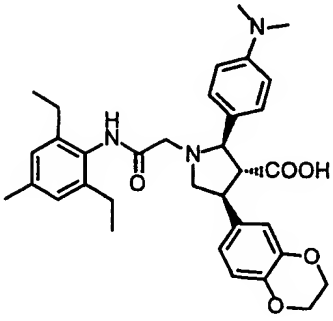

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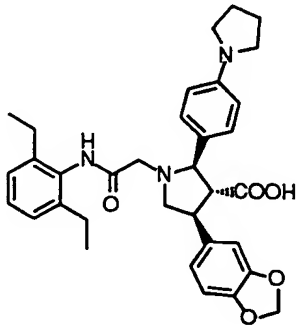

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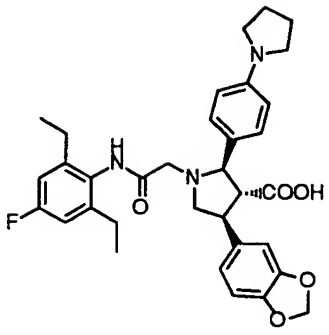

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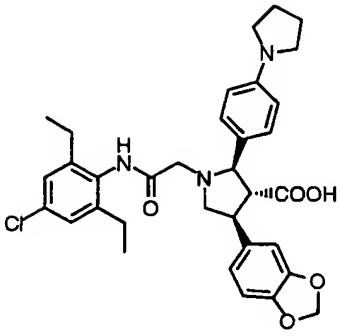

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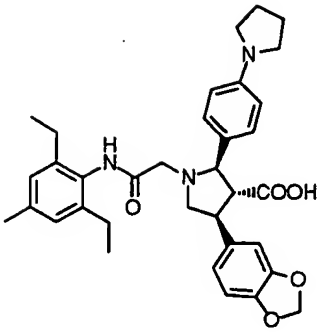

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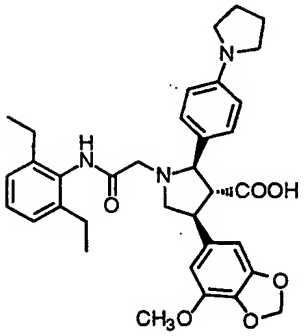

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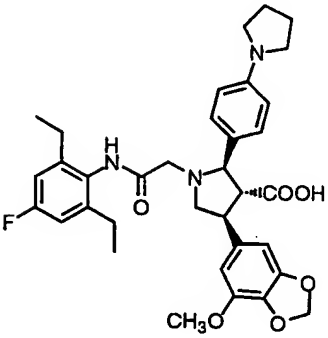

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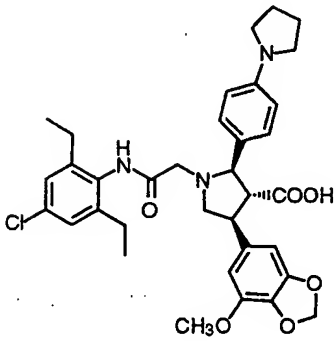

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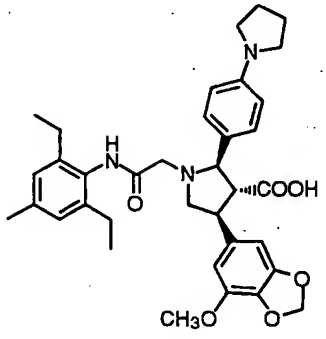

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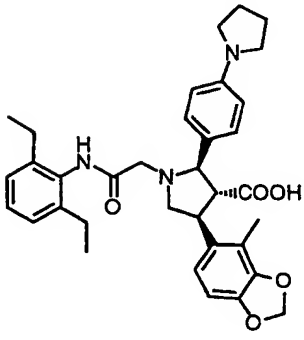

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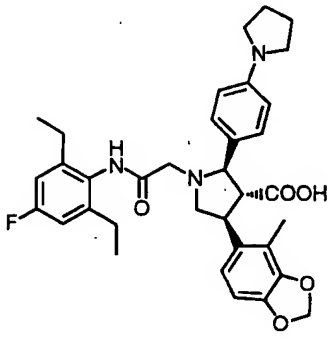

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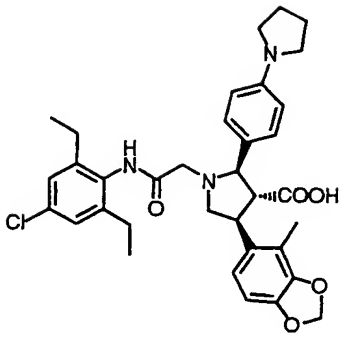

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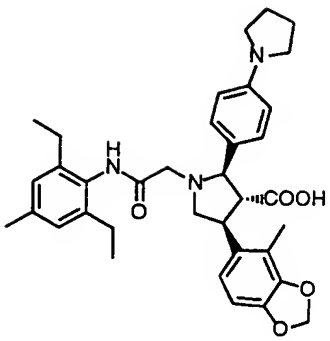

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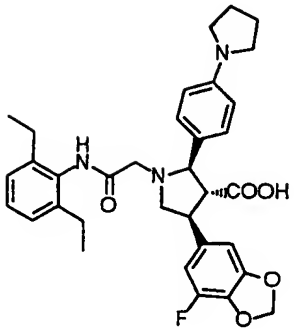

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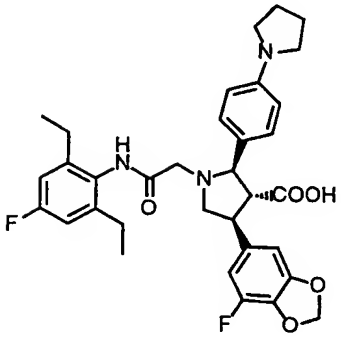

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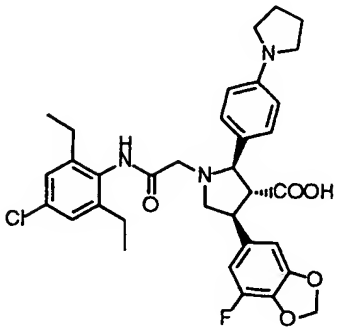

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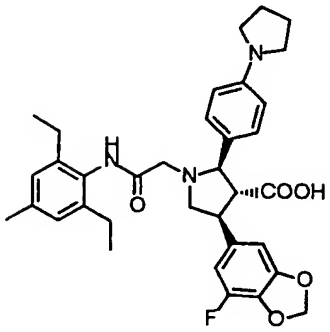

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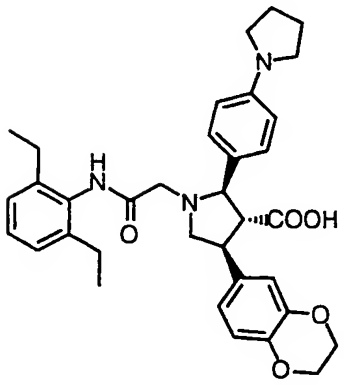

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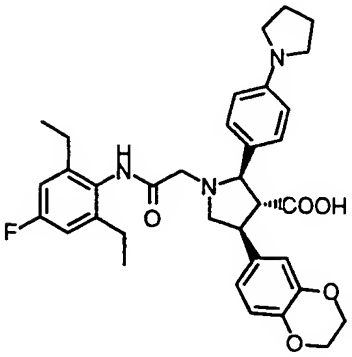

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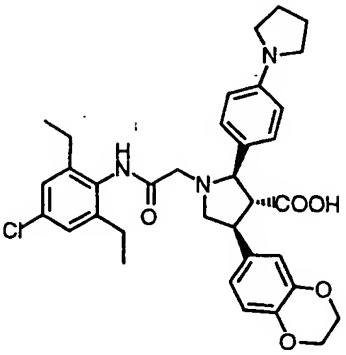

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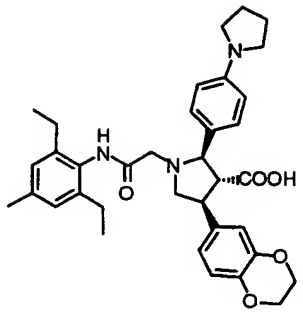

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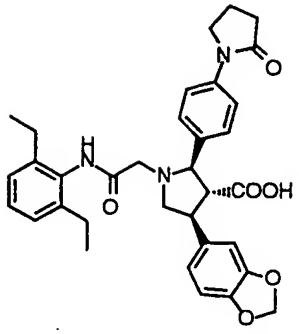

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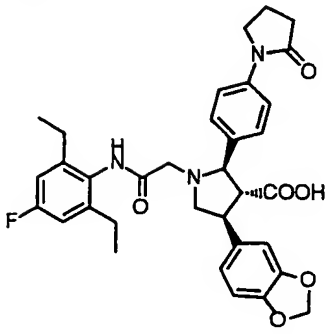

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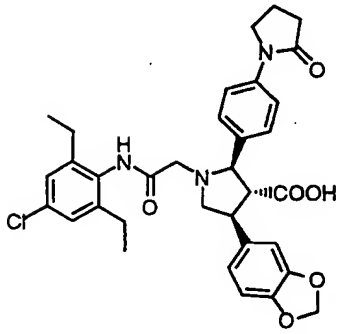

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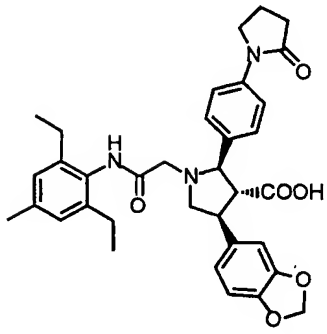

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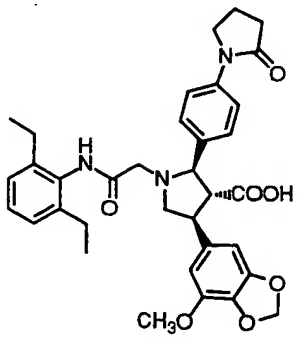

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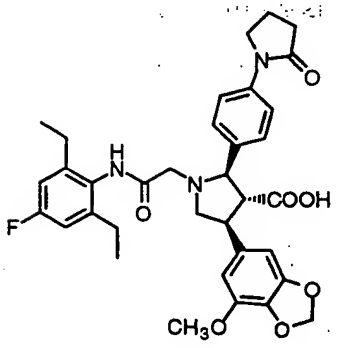

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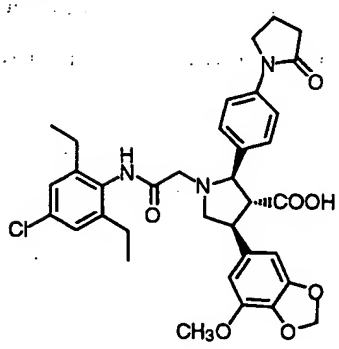

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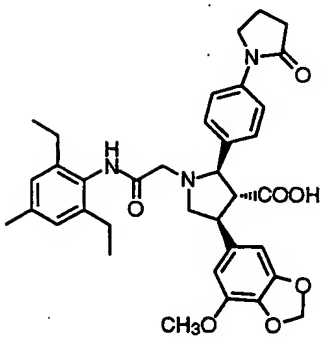

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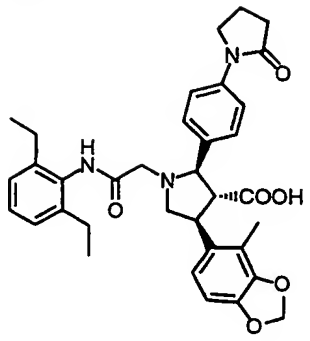

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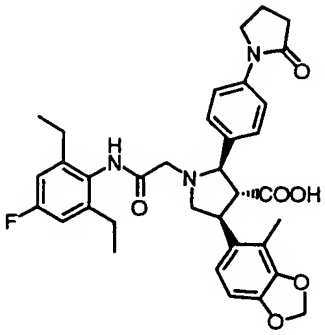

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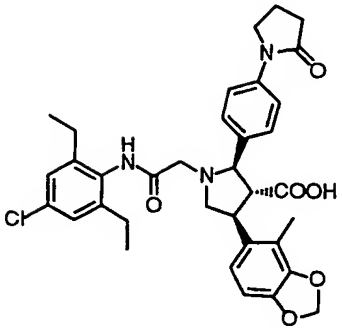

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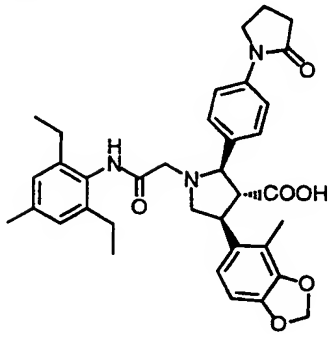

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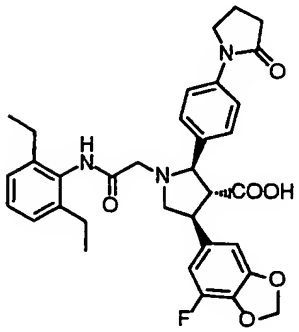

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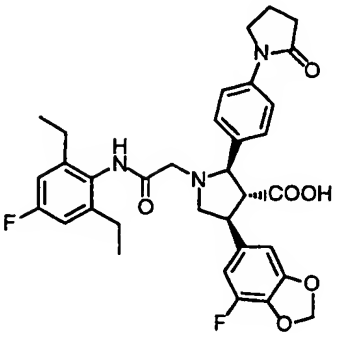

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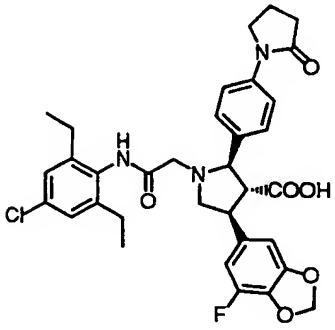

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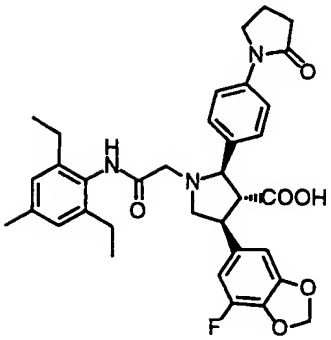

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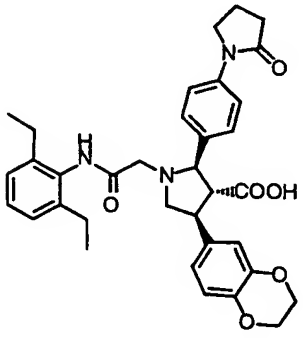

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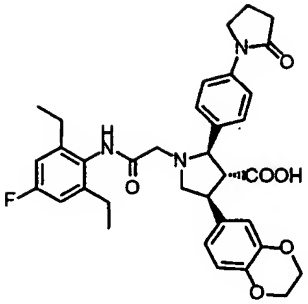

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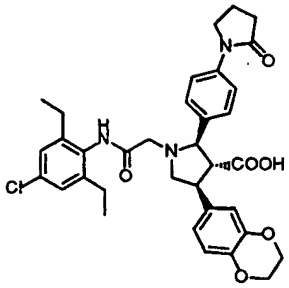

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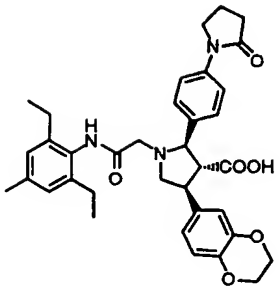

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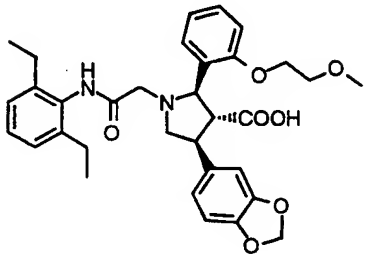

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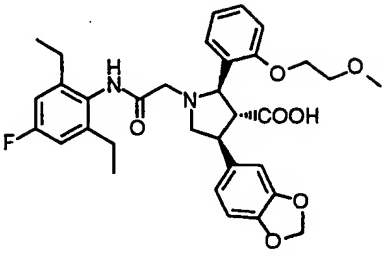

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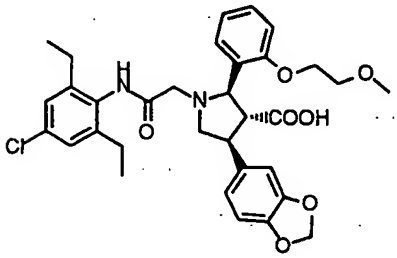

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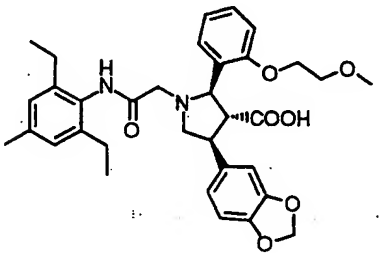

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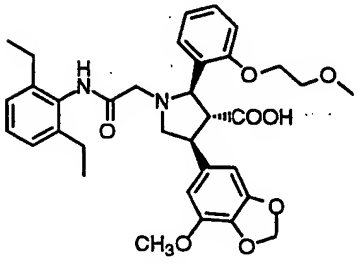

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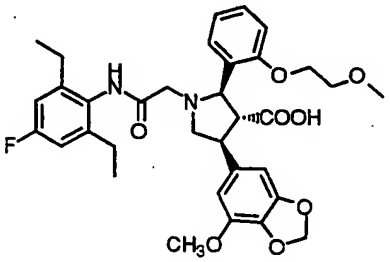

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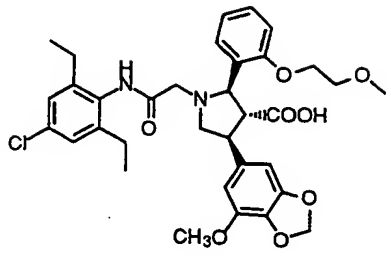

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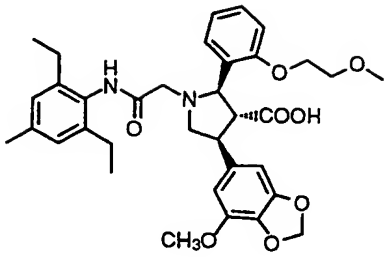

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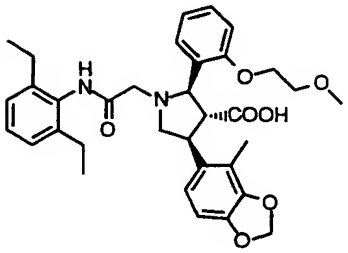

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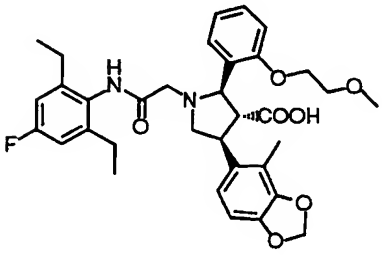

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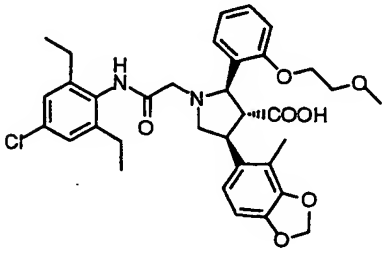

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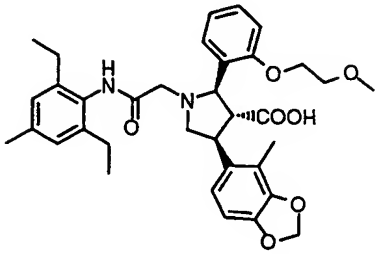

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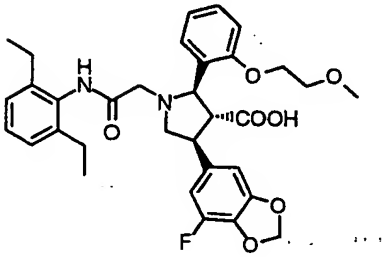

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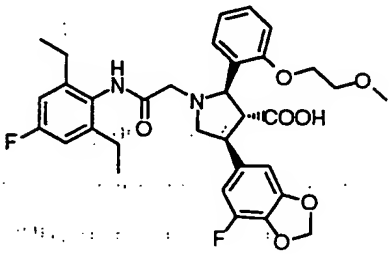

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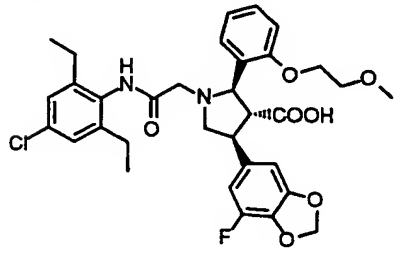

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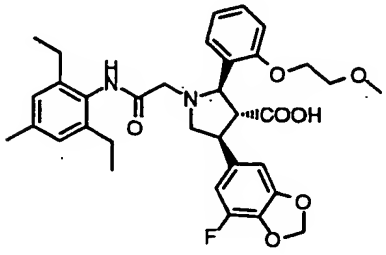

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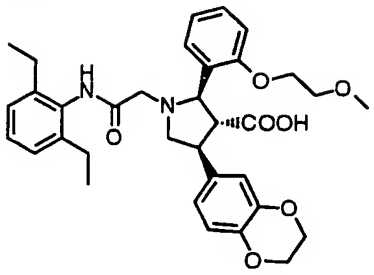

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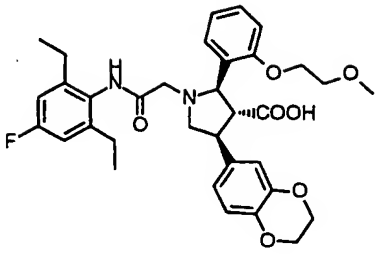

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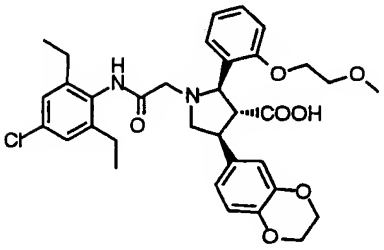

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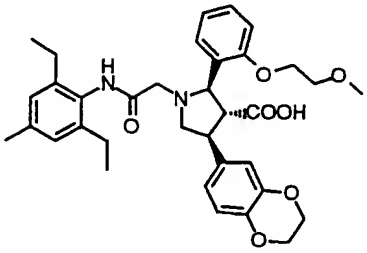

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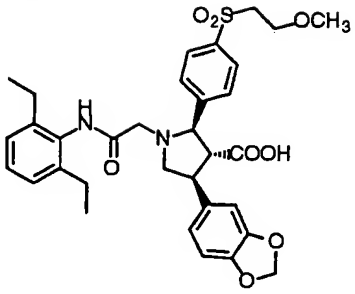

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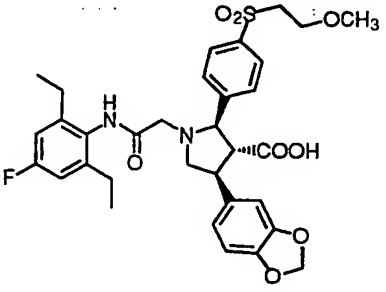

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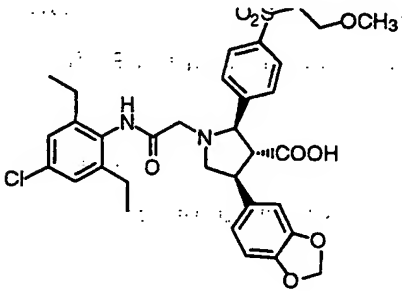

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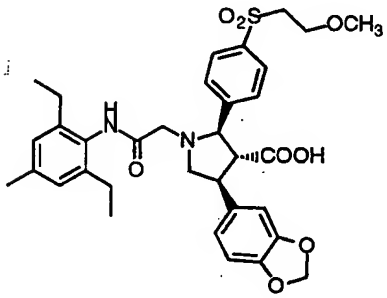

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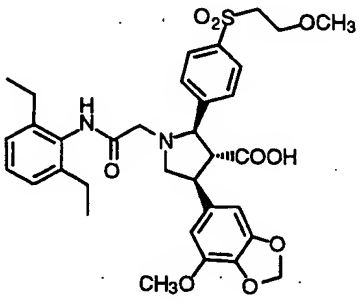

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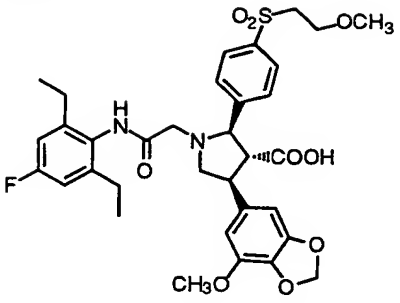

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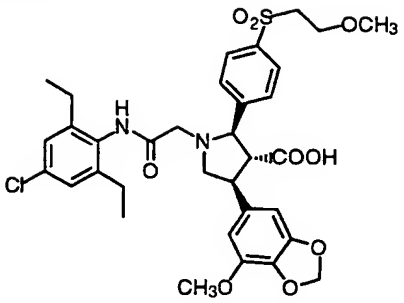

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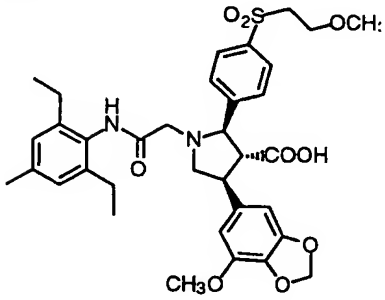

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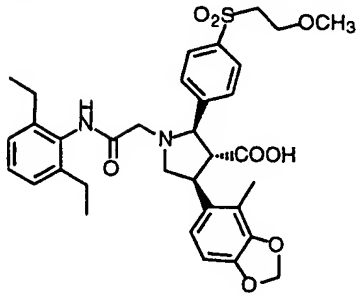

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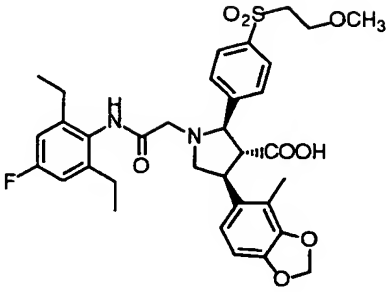

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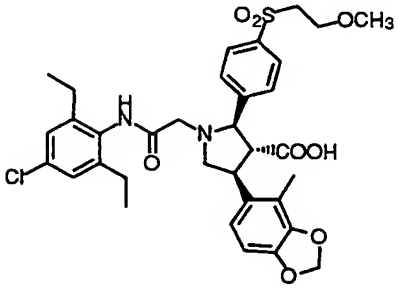

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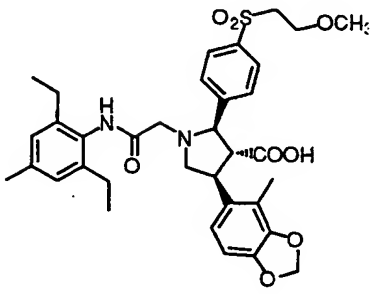

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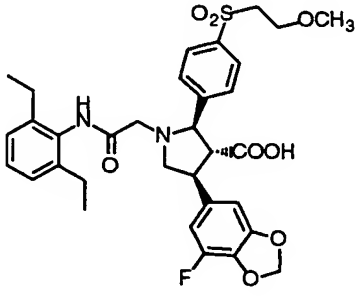

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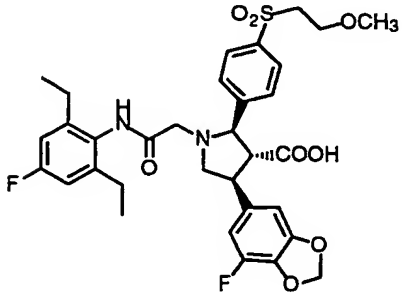

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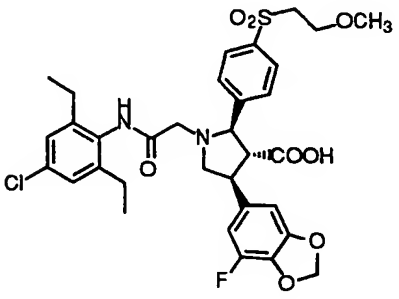

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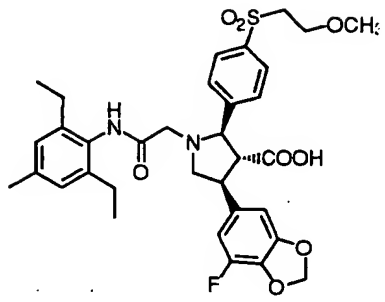

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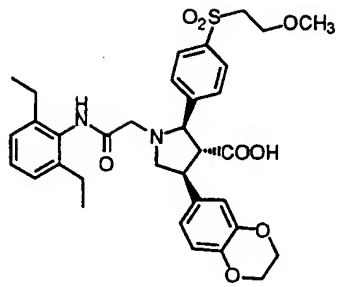

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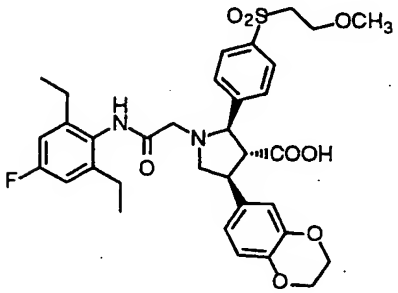

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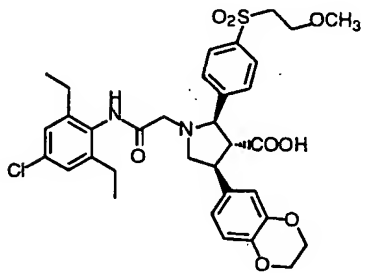

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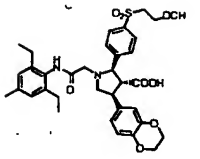

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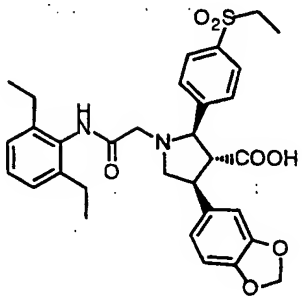

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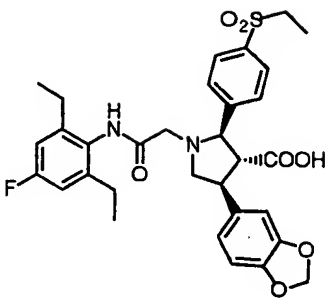

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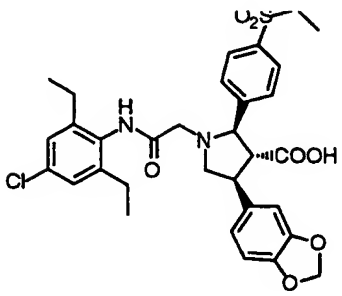

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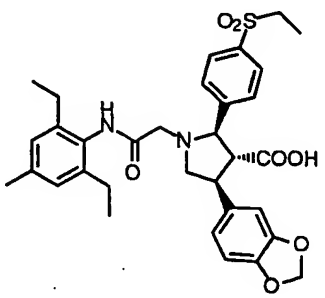

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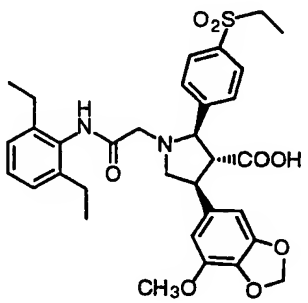

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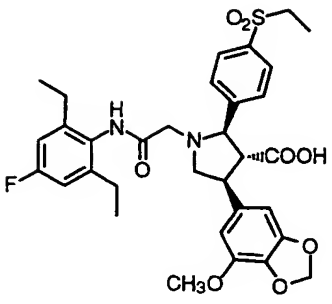

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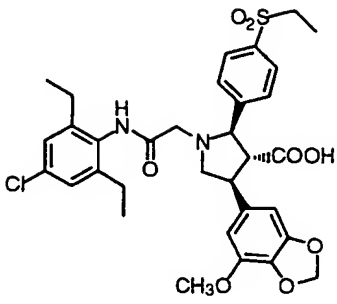

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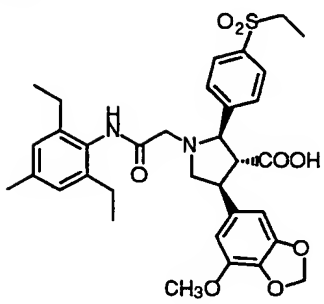

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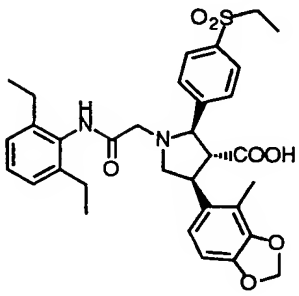

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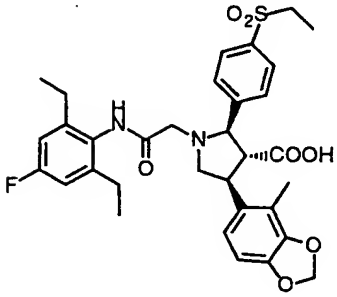

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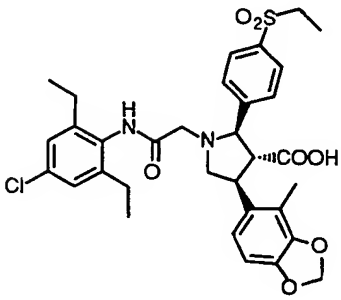

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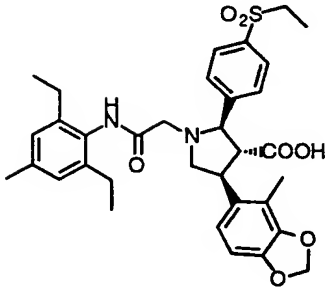

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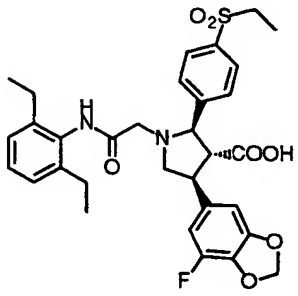

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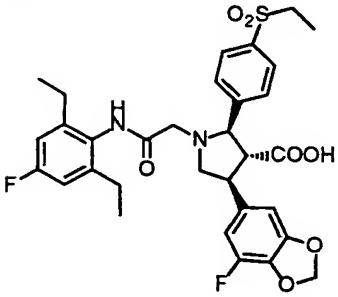

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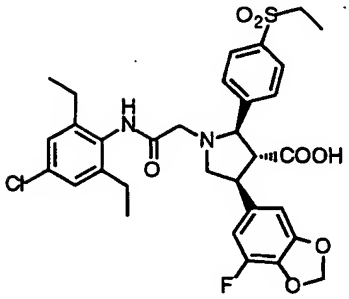

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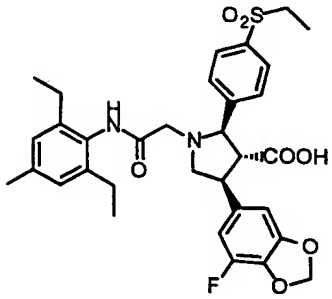

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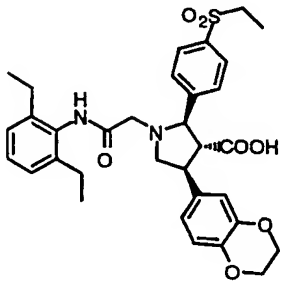

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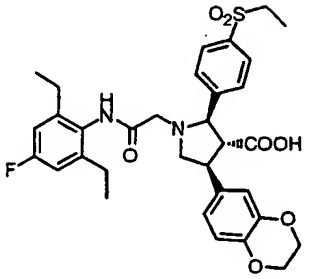

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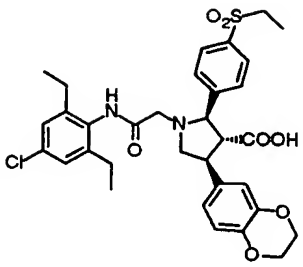

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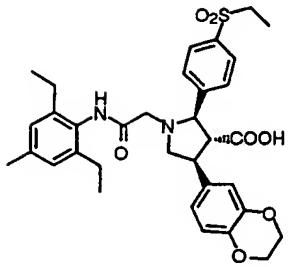

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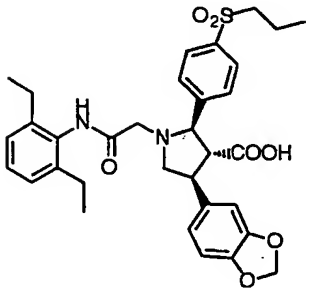

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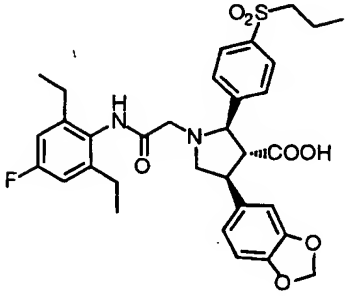

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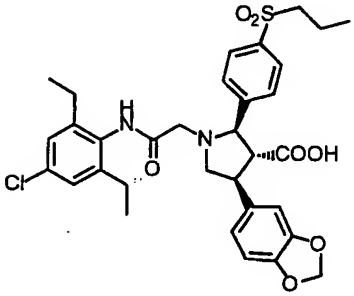

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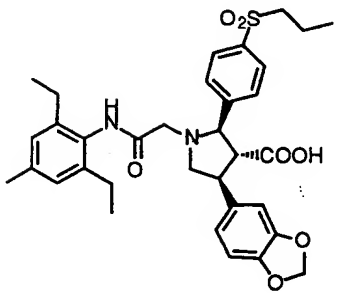

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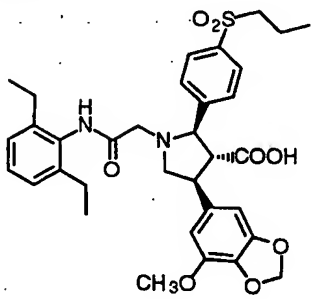

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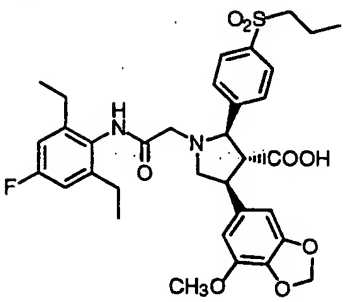

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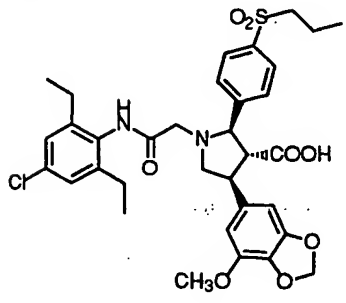

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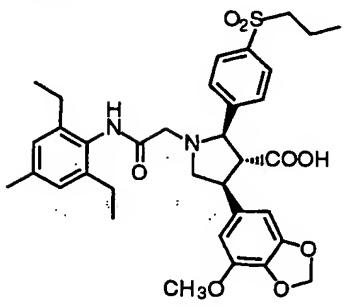

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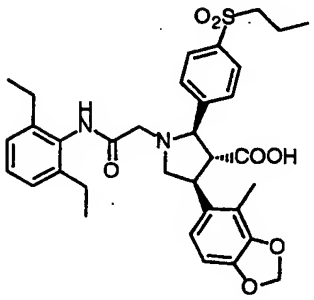

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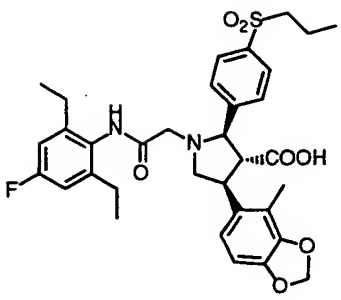

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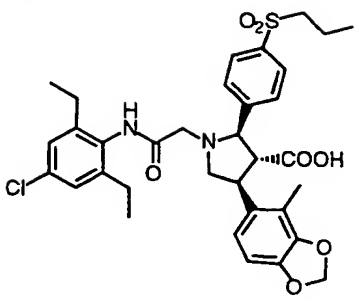

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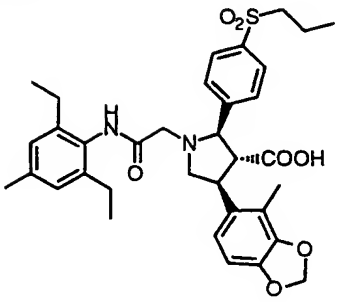

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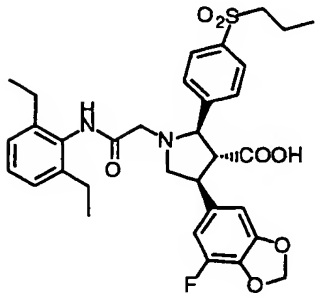

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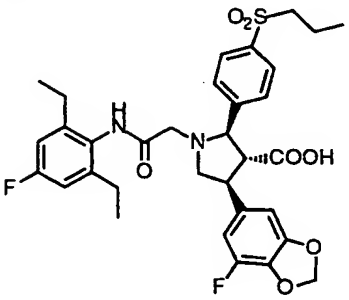

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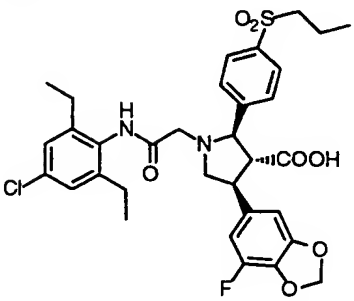

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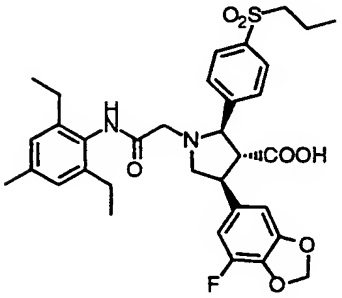

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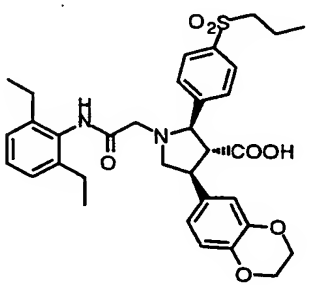

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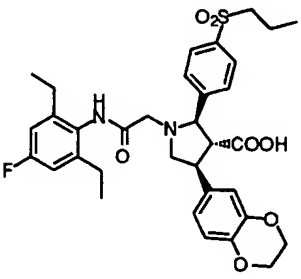

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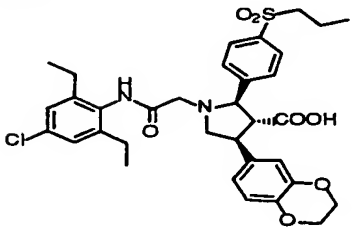

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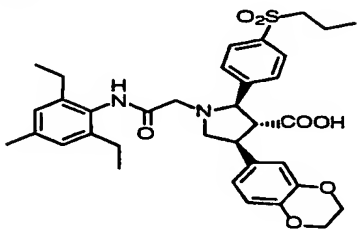


Example 858

trans,trans-2-(4-Methoxy)phenyl-4-(1,3-benzodioxol-5-yl)-1-((*N*-2,6-diethylphenyl)aminocarbonyl)amino-pyrrolidine3-carboxylic acid

Example 858A

Ethyl *trans,trans*-2-(4-methoxy)phenyl-4-(1,3-benzodioxol-5-yl)-1-amino-pyrrolidine-3-carboxylate

To a solution of 1.00g (2.71 mmol) ethyl *trans,trans*-2-(4-methoxy)phenyl-4-(1,3-benzodioxol-5-yl)-1-pyrrolidine-3-carboxylate in 6 mL of acetonitrile was added a solution of 1.18 g (10.4 mmol) of hydroxylamine-*O*-sulfonic acid in 2 mL of H_2O. The homogeneous reaction mixture warmed spontaneously, and was stirred for 20 minutes, then concentrated *in vacuo*. The residue was dissolved in 15 mL of ethyl acetate and extracted with 0.7M $NaHCO_3$ solution (2 x 25 mL), then brine (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated to a thick oil. This consisted of a mixture of the starting pyrrolidine and the corresponding 1-aminopyrrolidine. To a solution of 892 mg (2.2 mmol) of this oil in 10 mL of ethyl acetate was added 700 mg (3.21 mmol) of di-tertbutoxycarbonic anhydride. The mixture was stirred at ambient temperature for 30 min, then concentrated *in vacuo*. Silica gel chromatography, eluting with 30% EtOAc/Hex, gave 360 mg of ethyl *trans,trans*-2-(4-methoxy)phenyl-4-(1,3-benzodioxol-5-yl)-1-(tert-butoxycarbonyl)amino-pyrrolidine-3-carboxylate as a colorless oil. The desired product was slightly more polar than the tertbutoxycarbonylpyrrolidine. To 360 mg (0.768 mmol) of the Boc hydazine was added 2 mL of trifluoroacetic acid. After stirring for 2h at ambient temperature, the solvent was removed *in vacuo*. The residue was taken up in 10 mL of 0.6M $NaHCO_3$ solution and extracted with ethyl acetate (3 x 3 mL). The combined ethyl acetate layers were back extracted with brine (1 x 3 mL), dried over $MgSO_4$, filtered, and concentrated to 249 mg of a nearly colorless oil.

Example 858B

trans,trans-2-(4-Methoxy)phenyl-4-(1,3-benzodioxol-5-yl)-1-((*N*-2,6-diethylphenyl)aminocarbonyl)amino-pyrrolidine3-carboxylic acid

To an ice cooled solution of 100 mg (0.670 mmol) of 2,6-diethylaniline in 2 mL of THF and 0.4 mL of *N,N*-diisopropyl-*N*-ethylamine was added 66 mg (0.223 mmol) of triphosgene. The suspension was stirred at 0 °C for 10 min, then a solution of 249 mg (0.645 mmol) of ethyl *trans,trans*-2-(4-methoxy) phenyl-4-(1,3-benzodioxol-5-yl)-1-amino-pyrrolidine-3-carboxylate in 2 mL of THF was added. The mixture was stirred for 1.5 h, then a 20 mL of 0.6M $NaHCO_3$ solution was added. The suspension was extracted with ethyl acetate (3 x 5 mL), dried over $MgSO_4$, filtered, and concentrated to an oil which began to crystallize. This was taken up in a small amount of ethyl acetate, allowed to crystallize, and filtered to give 108 mg (30% from the hydrazine) of ethyl *trans,trans*-2-(4-Methoxy)phenyl-4-(1,3-benzodioxol-5-yl)-1-((*N*-2,6-diethylphenyl)aminocarbonyl) amino-pyrrolidine3-carboxylate. Hydrolysis of the ester was performed as described for other examples to give the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.00 (t, J=7.4, 6H), 2.33 (br t, J=7.0Hz, 4H), 2.90 (t, J=9.9Hz, 1H), 3.38-3.50 (m, 2H), 3.59 (m, 1H), 3.75 (s, 3H), 4.11 (d, J=10.3Hz, 1H), 5.98 (d, J=0.7Hz, 1H), 5.99 (d, J=1.1Hz, 1H), 6.82 (m, 2H), 6.89 (d, J=8.4Hz, 2H), 7.03 (d, J=7.0Hz, 2H), 7.12 (m, 1H), 7.33 (d, J=1.5Hz, 1H), 7.38 (s, 1H), 7.53 (d, J=8.8Hz, 2H), 8.02 (s, 1H), 12.3 (s, 1H); MS (CDI, *m/z*) 532 (MH^+). Anal. Calcd for $C_{30}H_{33}N_3O_6$: C, 67.78, H, 6.26, N, 7.90. Found: C, 67.71, H, 6.42, N, 7.82.

Example 859

[2R,3S,4S]-2[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 859A

Ethyl [2R,3S,4S]-2[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)- pyrrolidine-3-carboxylate

Ethyl *trans, trans*-2[4-(2-methoxyethoxy)]-4-(1,3-benzodioxol-5-yl)- pyrrolidine-3-carboxylate, from example 30, was reacted with di-*tert*-butyl dicarbonate, and the resulting product was hydrolyzed with NaOH to give *trans, trans* -2-[4-(2-methoxyethyl)]-4-(1,3-benzodioxol-5-yl)-1-(tert-butyloxycarbonyl)-pyrrolidine-3-carboxylic acid. This acid was resolved by salt formation with R-(+)- alpha methyl benzylamine. The resolved salt was washed with aqueous HCl to remove the resolving agent, then heated with HCl in ethanol at 70 degrees C for 18 hours to produce ethyl [2R,3S,4S]-2[4-(2-methoxyethoxy)]-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate, which was purified by chromatography on silica gel, eluting with ethyl acetate.

Example 859B

[2R,3S,4S]-2[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared as described in Example 30, employing the compound of Example 859A as starting material. ^{1}H NMR (300MHz, $CDCl_3$) δ 1.08 (t, J=7Hz, 6H), 2.43 (q, J=7Hz, 4H), 3.00 (d, J=11Hz, 1H), 3.05-3.15 (m, 2H), 3.44 (s, 3H), 3.46 (d, J=11Hz, 1H), 3.45-3.55 (m, 1H), 3.65-3.75 (m, 1H), 3.75-3.80 (m, 2H), 3.93 (d, J=7Hz, 1H), 4.12-4.17 (m, 2H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.75 (d, J=8Hz, 1H), 6.82 (dd, J=2Hz, 9Hz, 1H), 6.87 (d, J=2Hz, 1H), 6.95 (d, J=8Hz, 1H), 7.10 (d, J=6Hz, 2H), 7.19-7.24 (m, 1H), 7.37 (d, d=8Hz, 2H), 8.29 (s, 1H).

Example 860

trans,trans-2-(4-(2-Ethoxyethoxy))-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 30. ^1H NMR (300MHz, CD_3OD) δ 1.09 (t, J=7Hz, 6H), 1.23 (t, J=7Hz, 3H), 2.47 (q, J=7Hz, 4H), 3.4-3.55 (broad, 2H), 3.62 (q, J=7Hz, 2H), 3.6-3.9 (broad, 4H), 3.82 (m, 2H), 4.16 (m, 2H), 4.4 (broad, 1H), 5.93 (dd, J=1Hz,2Hz, 2H), 6.77 (d, J=8Hz, 1H), 6.90 (dd, J=2Hz, 8Hz, 1H), 7.04 (m, 3H), 7.12 (m, 2H), 7.22 (dd, J=7Hz,9Hz, 2H), 7.44 (m, 2H). MS (ESI+) m/e 589 ($M+H^+$). Anal. Calc for $C_{34}H_{40}N_2O_7$.0.5TFA: C, 65.11, H, 6.32, N 4.34. Found: C, 64.81, H, 6.36, N, 4.25.

Example 861

trans,trans-2-(4-(2-Isopropoxyethoxy))-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 30. ^1H NMR (300MHz, CD_3OD) δ 1.10 (t, J=7Hz, 6H), 1.18 (2, J=7Hz, 6H), 2.47 (q, J=7Hz, 4H), 3.4-3.55 (broad, 2H), 3.6-3.9 (broad, 4H), 3.75 (hept, 1H, J=7Hz), 3.82 (m, 2H), 4.17 (m, 2H), 4.4-4.5 (broad, 1H), 5.93 (broad s, 2H), 6.78 (d, J=8Hz, 1H), 6.90 (dd, J=2Hz, 8Hz, 1H), 7.05 (m, 3H), 7.12 (m, 2H), 7.20 (dd, J=7Hz,9Hz, 2H), 7.56 (m, 2H). MS (ESI+) m/e 603 ($M+H^+$). Anal. Calc for $C_{35}H_{42}N_2O_7$.0.6TFA: C, 64.79, H, 6.40, N, 4.17. Found: C, 64.40, H, 6.53, N, 4.20.

Example 862

trans,trans-2-(4-(2-Propoxy))-4-(1,4-benzodioxan-6-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1. ^1H NMR (300MHz, CD_3OD) δ 1.06 (t, J=7Hz, 3H), 1.09 (t, J=7Hz, 6H), 1.81 (m, 2H), 2.46 (q, J=7Hz, 4H), 3.3 (m, 2H), 3.4-3.5 (broad, 2H), 3.6-3.9 (broad, 4H), 3.95 (t, J=6Hz, 2H), 4.22 (s, 4H), 4.4 (broad, 1H), 6.80 (d, J=8Hz, 1H), 6.92 (dd, J=2Hz, 8Hz, 1H), 6.99 (m, 3H), 7.13 (m, 2H), 7.22 (dd, J=7Hz,9Hz, 2H), 7.44 (m, 2H). MS (ESI+) m/e 573 ($M+H^+$), 595 ($M+Na^+$). Anal. Calc for $C_{34}H_{48}N_2O_6$.0.6TFA: C, 65.95, H, 6.38, N 4.37. Found: C, 65.83, H, 6.40, N, 4.31.

Example 863

trans, trans-2[(4-butoxyphenyl)]-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by using the method of example 30 by substituting 1-bromobutane for 1-bromo-2-methoxyethane. ^1H NMR (300MHz, $CDCl_3$) δ 0.99 (t, J=7Hz, 3H), 1.08 (t, J=7Hz, 6H), 1.42-1.57 (m, 2H), 1.73-1.82 (m, 2H), 2.42 (q, J=7Hz, 4H), 3.00 (d, J=11Hz, 1H), 3.05-3.15 (m, 2H), 3.46 (d, J=11Hz, 1H), 3.50-3.55 (m, 1H), 3.65-3.75 (m, 1H), 3.93-4.00 (m, 3H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.75 (d, J=8Hz, 1H), 6.82 (dd, J=2Hz, 9Hz, 1H), 6.87 (d, J=2Hz, 1H), 6.93 (d, J=8Hz, 1H), 7.10 (d, J=7Hz, 2H), 7.19-7.24 (m, 1H), 7.37 (d, H=8Hz, 2H), 8.30 (s, 1H). MS (APCI+) m/e 573 ($M+H^+$). Anal. Calc for C34H40N2O6: C, 71.31 H, 7.04 N, 4.89. Found: C, 71.05 H, 7.09 N, 4.83

Example 864

trans, trans-2[4-{(2-methoxyethoxy)ethoxy}phenyl]-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by using the method of example 30 by substituting 1-bromo-2-(2-methoxyethoxy)ethane for 1-bromo-2-methoxyethane. ^{1}H NMR (300MHz, $CDCl_3$) δ 1.08 (t, J=7Hz, 6H), 2.43 (q, J=7Hz, 4H), 3.00 (d, J= 11 Hz, 1H), 3.05-3.15 (m, 2H), 3.40 (s, 3H), 3.46 (d, J=11Hz, 1H), 3.44-3.55 (m, 1H), 3.57-3.62 (m, 2H), 3.65-3.75 (m, 1H), 3.70-3.75 (m, 2H), 3.88 (t, J=6Hz, 2H), 3.93 (d, J=7Hz, 1H), 4.15 (t, J=7Hz, 2H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.75 (d, J=8Hz, 1H), 6.82 (dd, J=2Hz, 9Hz, 1H), 6.87 (d, J=2Hz, 1H), 6.93 (d, J=8Hz, 1H), 7.10 (d, J=7Hz, 2H), 7.19-7.24 (m, 1H), 7.37 (d, H=8Hz, 2H), 8.30 (s, 1H). MS (APCI+) m/e 619 ($M+H^+$). Anal. Calc for $C_{35}H_{42}N_2O_8$: C, 67.94 H, 6.84 N, 4.53. Found: C, 67.49 H, 6.90 N, 4.41.

Example 865

trans, trans-2[(3-propoxyphenyl)]-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by using the method of example 30 by substituting 1-bromopropane for 1-bromo-2-methoxyethane and methyl 3-hyroxybenzoate for ethyl 4-hyroxybenzoate. ^{1}H NMR (300MHz, $CDCl_3$) δ 1.02 (t, J=7Hz, 3H), 1.08 (t, J=7Hz, 6H), 1.75-1.87 (m, 2H), 2.43 (q, J=7Hz, 4H), 3.02 (d, J=11Hz, 1H), 3.09-3.20 (m, 3H), 3.48-3.56 (m, 2H), 3.65-3.75 (M, 1H), 3.90 (t, J=7Hz, 2H), 3.98 (d, J=8Hz, 1H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.75 (d, J=8Hz, 1H), 6.80-6.89 (m, 3H), 6.98-7.05 (m, 2H), 7.10 (d, J=8Hz, 2H), 7.19-7.32 (m, 2H), 8.30 (s, 1H). MS (APCI+) m/e 559 ($M+H^+$). Anal. Calc for $C_{33}H_{38}N_2O_6$: C, 70.94 H, 6.86 N, 5.01. Found: C, 70.65 H, 6.63 N, 4.92.

Example 866

trans,trans-2-(4-(2-methoxy)ethyl)phenyl-4-(1,3-benzodioxol-5-yl)-1-((*N*-2,6-diethylphenyl)aminocarbonyl)methyl-pyrrolidine-3-carboxylic acid

Example 866A

4-(2-methoxy)ethylbenzoic acid

To a 3-necked 50 mL flask fitted with two septa and a nitrogen balloon was added 800 mg (20 mmol) of 60% NaH dispersed in mineral oil. The oil was removed by washing and decanting with hexanes (3 x 5 mL), using a pipette and keeping a positive pressure of N_2 over the flask. Next, 5 mL of THF was added, the suspension was cooled with an ice bath, then a solution of 2.01 g (10.0 mmol) of 4-bromophenethanol in 5 mL of THF was added via cannula. The ice bath was removed, and the mixture was stirred for 10 min, then 700 mL (11 mmol) of iodomethane was added. The mixture was stirred at ambient temperature for 1h, then 1 mL of H_2O was added to quench the excess NaH. The reaction was poured into 50 mL of H_2O, then extracted with diethyl ether (3 x 20 mL). The combined ether layers were back extracted with brine (1 x 20 mL), dried over $MgSO_4$, filtered, and concentrated to 2.08g (97%) of a colorless oil. To a solution of 1.03 g (4.78 mmol) of the above 4-(2-methoxy)ethylbromobenzene in 10 mL of THF was added 400 mg of magnesium turnings, and a crystal of I_2. The mixture was heated to reflux under N_2 for 5 min, then cooled to ambient temperature. The Grignard reagent was transferred *via* syringe to a 50 mL 3-necked flask under N_2. A balloon of CO_2 was opened over the reaction, and the red color quickly faded to yellow. After stirring for 1h at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in 20 mL of H_2O and acidified with 12M HCl to pH=1, then extracted with diethyl ether (3 x 10 mL). The combined ether layers were back extracted with 2M NaOH (3 x 5 mL), then the combined NaOH layers were extracted with diethyl ether (2 x 5 mL). The basic layers were treated with 12M HCl until pH= 1, then the product was extracted with ethyl acetate (2 x 5 mL). The combined ethyl acetate layers were back extracted with brine (1 x 5 mL), dried over $MgSO_4$, filtered, and concentrated to 427 mg (50%)

of 4-(2-methoxy)ethylbenzoic acid as a yellow solid. The yellow impurity did not interfere with any subsequent reactions.

Example 866B

trans,trans-2-(4-(2-methoxy)ethyl)phenyl-4-(1,3-benzodioxol-5-yl)-1-((*N*-2,6-diethylphenyl)aminocarbonyl)methyl-pyrrolidine-3-carboxylic acid

Prepared according to the procedures described in Example 1. ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.00 (t, J=7.5Hz, 6H), 2.40 (q, J=7.5Hz, 4H), 2.66 (t, J=8.3Hz, 1H), 2.79 (t, J=6.8Hz, 2H), 2.87 (d, J=15.6Hz, 1H), 3.00 (t, J=9.2Hz, 1H), 3.20 (d, J=15.9Hz, 1H), 3.24 (s, 3H), 3.42-3.47 (m, 1H), 3.53 (t, J=6.9Hz, 1H), 3.60 (m, 1H), 3.91 (d, J=9.5Hz, 1H), 5.94 (s, 2H), 6.76 (d, J=7.8Hz, 1H), 6.84 (dd, J=1.4Hz, 8.1Hz, 1H), 7.08 (d, J=7.5Hz, 2H), 7.17 (d, J=6.4Hz, 3H), 7.22 (d, J=1.4Hz, 1H), 7.51 (d, J=8.1Hz, 2H), 9.21 (s, 1H); MS (CDI *m/z*) 559 (MH^+); Anal. Calcd for $C_{33}H_{38}N_2O_6 \cdot 0.20\ H_3PO_4$. C, 68.54, H, 6.73, N, 4.84. Found C, 68.28, H, 6.46, N, 4.82.

Example 867

trans, trans-2[3-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by using the method of example 30 by substituting methyl 3-hydroxybenzoate for methyl 4-hyroxybenzoate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J=7Hz, 6H), 2.43 (q, J=7Hz, 4H), 3.00-3.20 (m, 3H), 3.42 (s, 3H), 3.50 (d, J=11Hz, 1H), 3.53-3.59 (m, 1H), 3.65-3.75 (m, 1H), 3.75 (t, J=6Hz, 2H), 3.98 (d, J=8Hz, 1H), 4.11 (t, J=6Hz, 2H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.75 (d, J=8Hz, 1H), 6.80-6.89 (m, 3H), 7.05-7.10 (m, 2H), 7.10 (d, J=8Hz, 2H), 7.19-7.32 (m, 2H), 8.30 (s, 1H). MS (APCI+) m/e 575 ($M+H^+$) Anal. Calc for C33H38N2O7: C, 68.97 H, 6.67 N, 4.87. Found: C, 68.78 H, 6.84 N, 4.72.

Example 868

trans, trans-2[(2-methyl-4-propoxyphenyl)]-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 868A

Ethyl (4-propoxy-2-methylbenzoyl) acetate

4-Hydroxy-2-methylacetophenone was reacted with 1-bromopropane and potassium carbonate in dimethylformamide to give 4-propoxy-2-methylacetophenone. This compound was reacted with diethyl carbonate, using the method described in example 15B to provide the title compound.

Example 868B

trans, trans-2[(2-methyl-4-propoxyphenyl)]-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Prepared using the procedures described in Example 30, employing the compound of Example 868A as starting material. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, J=7Hz, 3H), 1.08 (t, J=7Hz, 6H), 1.75-1.85 (m, 2H), 2.33 (s, 3H), 2.40-2.48 (q, J=7Hz, 4H), 2.98 (d, J=11Hz, 1H), 3.06-3.18 (m, 2H), 3.39 (d, J=11Hz, 1H), 3.50-3.58 (m, 1H), 3.65-3.75 (m, 1H), 3.90 (t, J=7Hz, 2H), 4.28 (d, J=8Hz, 1H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.70-6.88 (m, 5H), 7.08-7.25 (m, 3H), 7.48 (d, J=8Hz, 1H), 8.28 (s, 1H). MS (APCI+) m/e 773 ($M+H^+$). Anal. Calc for $C_{34}H_{40}N_2O_6$: C, 70.56 H, 7.79 N, 4.33. Found: C, 70.16 H, 7.70 N, 4.26.

Example 869

trans,trans-2-(4-(3-methoxy)propyl)phenyl-4-(1,3-benzodioxol-5-yl)-1-((*N*-2,6-diethylphenyl)aminocarbonyl)methyl-pyrrolidine-3-carboxylic acid

Example 869A

4-(3-methoxy)propylbenzoic acid

To a mixture of 10.0g (46.5 mmol) of methyl 4-bromobenzoate, 325 mg (1.45 mmol) of palladium(II)acetate, 15.1g (51.0 mmol) of tetrabutylammonium chloride, and 13.7g (140 mmol) of potassium acetate was added 200 mL of DMF. The mixture was degassed and back filled with N_2 twice, then 10 mL of allyl methyl ether was added. The reaction was stirred at 50 °C for 6h, then at ambient temperature for 66h. The reaction was monitored by TLC (20% ethyl acetate/ hexanes). Additional Pd catalyst (319 mg) was added after this time, as some bromoester remained. After heating at 50 °C under N_2 for 2h, the reaction was poured into 1L of water, and this suspension was divided into two portions for ease of handling. Each was extracted with diethyl ether (3 x 100 mL), then each set of ether layers was back extracted with water (1 x

100 mL), saturated *aq.* $NaHCO_3$ solution (1 x 100 mL), and brine (1 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The combined crude yield of methyl 4-(3-methoxy-1-propenyl)benzoate and methyl 4-(3-methoxy-2-propenyl)benzoate was 9.17 g. To a mixture of 8.57g (41.6 mmol) of the above and 400 mg of 10% Pd-C was added 75 mL of THF. The mixture was stirred at ambient temperature under 1 atm of H_2 for 2h, then the catalyst was filtered away, and the solvent was removed *in vacuo*. Purification via a 15% ethyl acetate/hexanes column gave 3.35 g (39%) of methyl 4-(3-methoxypropyl)benzoate as a colorless oil. This material was combined with 20 mL of 1.39M NaOH in 5:1 ethanol:H_2O. The reaction was heated at reflux for 30 min, then concentrated *in vacuo*. The residue was taken up in 25 mL of H_2O, then 40 mL of 1M HCl was added. The mixture was extracted with diethyl ether (3 x 25 mL), then the combined ether layers were back extracted with brine (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to 3.03 g (97%) of 4-(3-methoxy)propylbenzoic acid as a white solid.

Example 869

trans,trans-2-(4-(3-methoxy)propyl)phenyl-4-(1,3-benzodioxol-5-yl)-1-((*N*-2,6-diethylphenyl)aminocarbonyl)methyl-pyrrolidine-3-carboxylic acid

Prepared according to the procedures of Example 1. ^1H NMR (300 MHz, d_6-DMSO) δ 1.00 (t, J=7.5Hz, 6H), 1.80 (m, 2), 2.41 (q, J=7.5Hz, 4H), 2.62 (t, J=7.7Hz, 2H), 2.86 (t, J=9.7Hz, 1H), 2.93 (d, J=15.8Hz, 1H), 3.11 (t, J=9.6Hz, 1H), 3.18 (d, J=16.2Hz, 1H), 3.23 (s, 3H), 3.31-3.40 (m, 2H), 3.50 (m, 1H), 3.53 (m, 1H), 3.95 (d, J=9.9Hz, 1H), 5.98 (s, 2H), 6.80 (dd, J=1.5Hz, 8.1Hz, 1H), 6.85 (dd, J=1.5Hz, 8.1Hz, 1H), 7.10 (d, J=7.0Hz, 2H), 7.18 (m, 3H), 7.28 (d, J=1.5Hz, 1H), 7.53 (d, J=8.1Hz, 1H), 9.28 (s, 1H); MS (CDI *m/z*) 571 (MH^+); Anal. Calcd for $C_{34}H_{40}N_2O_6 \cdot 0.05H_3PO_4$: C, 70.70, H, 7.00, N, 4.85. Found: C, 70.68, H, 6.91, N, 4.62.

As an indication that the compounds described herein act through binding to endothelin receptors, the compounds have been evaluated for their ability to displace endothelin from its receptor.

Binding Assay
ET_B Receptor

Preparation of membranes from Porcine cerebellum:

Porcine cerebellum was homogenized in 25 volumes (w/v) of 10 mM Hepes (pH 7.4) containing 0.25 M sucrose and protease inhibitors (3 mM EDTA, 0.1 mM PMSF, and 5 µg/ml Pepstatin A) by 3-10 sec polytron at 13,500 rpm with 10 sec intervals. The mixture was centrifuged at 1000xg for 10 min. The supernatant was collected and centrifuged at 30,000xg for 30 min. The precipitate was resuspended in Buffer A (20 mM Tris, 100 mM NaCl, 10 mM $MgCl_2$, pH 7.4) containing the aforementioned protease inhibitors and centrifuged again. The final pellet was resuspended in Buffer A containing protease inhibitors and stored at -80°C until used. Protein content was determined by the Bio-Rad dye-binding protein assay.

[^{125}I]ET-3 binding to membranes:

Binding assays were performed in 96-well microtiter plates pretreated with 0.1% BSA. Membranes prepared from cells were diluted ~100 fold in Buffer B (20 mM Tris, 100 mM NaCl, 10 mM $MgCl_2$, pH 7.4, with 0.2% BSA, 0.1 mM PMSF, 5 µg/mL Pepstatin A, 0.025% bacitracin, and 3 mM EDTA) to a final concentration of 0.2 mg/mL of protein. In competition studies, membranes (0.02 mg) were incubated with 0.1 nM of [^{125}I]ET-3 in Buffer B (final volume: 0.2 mL) in the presence of increasing concentrations of unlabeled ET-3 or a test compound for 4 hours at 25 °C. After incubation, unbound ligands were separated from bound ligands by a vacuum filtration method using glass-fiber filter strips in PHD cell harvesters (Cambridge Technology, Inc., MA), followed by washing the filter strips with saline (1 mL) for three times. Nonspecific binding was determined in the presence of 1 µM ET-1. The data are shown in Table 1. The per cent inhibition at a concentration of 1 µM is shown. The data show that the compounds of the invention bind to the endothelin receptor.

Table 1
Binding Data

Example	% Inhibition of ET_B at 1 μM	Example	% Inhibition of ET_B at 1 μM
1	96.4	2	91.5
3	82.1	4	94.0
5	96.5	6	92.9
7	94.5	8	93.6
9	94.8	10	95.2
11	96.0	12	96.7
13	91.3	14	96.6
15	93.4	16	92.3
17	97.1	18	94.9
19	94.9	20	95.5
21	97.1	22	95.3
23	99.1	24	93.3
25	95.7	26	98.0
27	98.8	28	97.2
29	94.7	30	97.4
858	98.3	859	95.6
860	93.0	861	96.7
862	92.8	863	92.7
864	96.3	865	92.1
866	92.0	867	93.5
868	96.1	869	98.9

The ability of the compounds of the invention to lower blood pressure can be demonstrated according to the methods described in Matsumura, et al., Eur. J. Pharmacol. 185 103 (1990) and Takata, et al., Clin. Exp. Pharmacol. Physiol. 10 131 (1983).

The ability of the compounds of the invention to treat congestive heart failure can be demonstrated according to the method described in Margulies, et al., Circulation 82 2226 (1990).

The ability of the compounds of the invention to treat myocardial ischemia can be demonstrated according to the method described in Watanabe, et al., Nature 344 114 (1990).

The ability of the compounds of the invention to treat coronary angina can be demonstrated according to the method described in Heistad, et al., Circ. Res. 54 711 (1984).

The ability of the compounds of the invention to treat cerebral vasospasm can be demonstrated according to the methods described in Nakagomi, et al., J. Neurosurg. 66 915 (1987) or Matsumura, et al., Life Sci. 49 841-848 (1991).

The ability of the compounds of the invention to treat cerebral ischemia can be demonstrated according to the method described in Hara et al., European. J. Pharmacol. 197: 75-82, (1991).

The ability of the compounds of the invention to treat acute renal failure can be demonstrated according to the method described in Kon, et al., J. Clin. Invest. 83 1762 (1989).

The ability of the compounds of the invention to treat chronic renal failure can be demonstrated according to the method described in Benigni, et al., Kidney Int. 44 440-444 (1993).

The ability of the compounds of the invention to treat gastric ulceration can be demonstrated according to the method described in Wallace, et al., Am. J. Physiol. 256 G661 (1989).

The ability of the compounds of the invention to treat cyclosporin-induced nephrotoxicity can be demonstrated according to the method described in Kon, et al., Kidney Int. 37 1487 (1990).

The ability of the compounds of the invention to treat endotoxin-induced toxicity (shock) can be demonstrated according to the method described in Takahashi, et al., Clinical Sci. 79 619 (1990).

The ability of the compounds of the invention to treat asthma can be demonstrated according to the method described in Potvin and Varma, Can. J. Physiol. and Pharmacol. 67 1213 (1989).

The ability of the compounds of the invention to treat transplant-induced atherosclerosis can be demonstrated according to the method described in Foegh, et al., Atherosclerosis 78 229-236 (1989).

The ability of the compounds of the invention to treat atherosclerosis can be demonstrated according to the methods described in Bobik, et al., Am. J. Physiol. 258 C408 (1990) and Chobanian, et al., Hypertension 15 327 (1990).

The ability of the compounds of the invention to treat LPL-related lipoprotein disorders can be demonstrated according to the method described in Ishida, et al., Biochem. Pharmacol. 44 1431-1436 (1992).

The ability of the compounds of the invention to treat proliferative diseases can be demonstrated according to the methods described in Bunchman ET and CA Brookshire, Transplantation Proceed. 23 967-968 (1991); Yamagishi, et al., Biochem. Biophys. Res. Comm. 191 840-846 (1993); and Shichiri, et al., J. Clin. Invest. 87 1867-1871 (1991). Proliferative diseases include smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma, prostatic hyperplasia, cardiac hyperplasia, restenosis following arterial injury or other pathologic stenosis of blood vessels.

The ability of the compounds of the invention to treat acute or chronic pulmonary hypertension can be demonstrated according to the method described in Bonvallet et al., Am. J. Physiol. 266 H1327 (1994). Pulmonary hypertension can be associated with congestive heart failure, mitral valve stenosis, emphysema, lung fibrosis, chronic obstructive pulmonary disease (COPD), acute repiratory distress syndrome (ARDS), altitude sickness, chemical exposure, or may be idiopathic.

The ability of the compounds of the invention to treat plaletet aggregation, and thrombosis, can be demonstrated according to the method described in McMurdo et al. Eu. J. Pharmacol. 259 51 (1994).

The ability of the compounds of the invention to treat cancers can be demonstrated according to the method described in Shichiri, et al., J. Clin. Invest. 87 1867 (1991).

The ability of the compounds of the invention to treat adenocarcinoma can be demonstrated according to the method described in Nelson, et al., Nature Medicine, 1, (9), 944 (1995).

The ability of the compounds of the invention to treat IL-2 (and other cytokine) mediated cardiotoxicity and vascular permeability disorders can be demonstrated

according to the method described in Klemm et al., Proc. Nat. Acad. Sci. 92 2691 (1995).

The ability of the compounds of the invention to treat nociception can be demonstrated according to the method described in Yamamoto et al., J. Pharmacol. Exp. Therap. 271 156 (1994).

The ability of the compounds of the invention to treat colitis can be demonstrated according to the method described in Hogaboam et al (EUR. J. Pharmacol. 1996, 309, 261-269).

The ability of the compounds of the invention to treat ischemia-repurfusion injury in kidney transplantation can be demonstrated according to the method described in Aktan et al (Transplant Int 1996, 9, 201-207).

The ability of the compounds of the invention to treat angina, pulmonary hypertension, Raynaud's disease, and migraine can be demonstrated according to the method described in Ferro and Webb (Drugs 1996, 51,12-27).

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by

reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful for antagonizing endothelin in a human or other mammal. In addition, the compounds of the present invention are useful (in a human or other mammal) for the treatment of hypertension, acute or chronic pulmonary hypertension, Raynaud's disease, congestive heart failure, myocardial ischemia, reperfusion injury, coronary angina, cerebral ischemia, cerebral vasospasm, chronic or acute renal failure, non-steroidal antiinflammatory drug induced gastric ulceration, cyclosporin induced nephrotoxicity, endotoxin-induced toxicity, asthma, fibrotic or proliferative diseases, including smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma, prostatic hyperplasia, cardiac hyperplasia, restenosis following arterial injury or other pathologic stenosis of blood vessels, LPL-related lipoprotein disorders, transplantation-induced atherosclerosis or atherosclerosis in general, platelet aggregation, thrombosis, cancers, adenocarcinoma, IL-2 and other cytokine mediated cardiotoxicity and permeability disorders, colitis, migraine, and nociception.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more usually 0.1 to 100 mg/kg for oral administration or 0.01 to 10 mg/kg for parenteral administration. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be formulated according to the known art. The title compound was prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capabale of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

A representative solid dosage form, for example, a tablet or a capsule, comprises:

Compound of the invention:	35% w/w
Starch, Pregelatinized, NF	50% w/w
Microcrystalline Cellulose, NF	10% w/w
Talc, Powder, USP	5% w/w

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more cardiovascular agents independently selected from diuretics, adrenergic blocking agents, vasodilators, calcium channel blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, potassium channel activators and other cardiovascular agents.

Representative diuretics include hydrochlorothiazide, chlorothiazide, acetazolamide, amiloride, bumetanide, benzthiazide, ethacrynic acid, furosemide, indacrinone, metolazone, spironolactone, triamterene, chlorthalidone and the like or a pharmaceutically acceptable salt thereof.

Representative adrenergic blocking agents include phentolamine, phenoxybenzamine, prazosin, terazosin, tolazine, atenolol, metoprolol, nadolol,

propranolol, timolol, carteolol and the like or a pharmaceutically acceptable salt thereof.

Representative vasodilators include hydralazine, minoxidil, diazoxide, nitroprusside and the like or a pharmaceutically acceptable salt thereof.

Representative calcium channel blockers include amrinone, bencyclane, diltiazem, fendiline, flunarizine, nicardipine, nimodipine, perhexilene, verapamil, gallopamil, nifedipine and the like or a pharmaceutically acceptable salt thereof.

Representative renin inhibitors include enalkiren, zankiren, RO 42-5892, PD-134672 and the like or a pharmaceutically acceptable salt thereof.

Representative angiotensin II antagonists include DUP 753, A-81988 and the like.

Representative ACE inhibitors include captopril, enalapril, lisinopril and the like or a pharmaceutically acceptable salt thereof.

Representative potassium channel activators include pinacidil and the like or a pharmaceutically acceptable salt thereof.

Other representative cardiovascular agents include sympatholytic agents such as methyldopa, clonidine, guanabenz, reserpine and the like or a pharmaceutically acceptable salt thereof.

The compounds of the invention and the cardiovascular agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents.

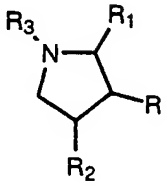
When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, processes, compositions and methods. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

CLAIMS

What is claimed is:

1. A compound of the formula:



wherein

R is $-(CH_2)_m$-W wherein m is an integer from 0 to 6 and W is

(a) $-C(O)_2$-G wherein G is hydrogen or a carboxy protecting group,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

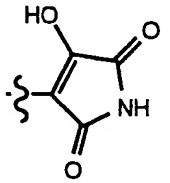
(i) hydroxy,

(j) alkoxy,

(k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,

(m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,

(n) 

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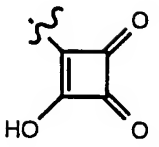
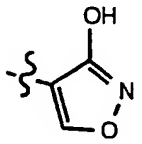
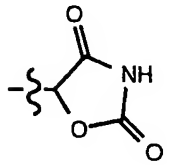
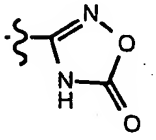
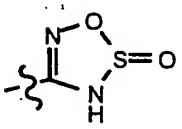
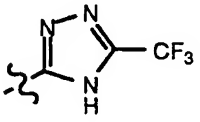
(o)  ,

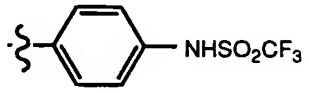
(p)  ,

(q)  ,

(r)  ,

(s)  ,

(t)  , or

(u)  ;

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N\text{-}R_{cc}$- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

R_3 is $R_4\text{-}C(O)\text{-}R_5$- or $R_6\text{-}S(O)_2\text{-}R_7$-

wherein R_5 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) $-N(R_{20})-R_8-$ or $-R_{8a}-N(R_{20})-R_8-$

wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene and alkenylene and

R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl or cycloalkylalkyl or (v) $-O-R_9-$ or $-R_{9a}-O-R_9-$

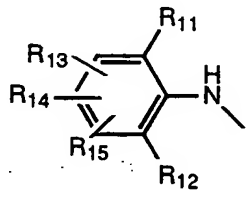
wherein R_9 and R_{9a} are independently selected from alkylene;

R_7 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{21})-R_{10}-$ or $-R_{10a}-N(R_{21})-R_{10}-$

wherein R_{10} and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and

R_{21} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

wherein R_4 and R_6 are



(i) ,

wherein R_{11} and R_{12} are independently selected from the group consisting of loweralkyl, cyano, alkoxy, halo, haloalkyl, and phenyl, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano or

(ii) heterocyclic(amino),

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein

R_3 is $R_4-C(O)-R_5-$ wherein R_4 is as defined therein and R_5 is alkylene or R_3 is $R_6-S(O)_2-R_7-$ wherein R_7 is alkylene and R_6 is as defined therein.

3. The compound according to Claim 1 wherein

R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group or R is tetrazolyl or R is $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl,

R_1 and R_2 are independently selected from

(i) loweralkyl, (ii) cycloalkyl, (iii) substituted or unsubstituted aryl and (iv) substituted or unsubstituted heterocyclic, and

R_3 is $R_4-C(O)-R_5-$ wherein R_4 is as defined therein and R_5 is alkylene or R_3 is $R_6-S(O)_2-R_7-$ wherein R_7 is alkylene and R_6 is as defined therein.

4. The compound according to Claim 1 wherein

R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl,

R_1 is (i) alkoxyalkyl, (ii) cycloalkyl, (iii) phenyl, (iv) pyridyl, (v) furanyl or (vi) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is $R_4-C(O)-R_5-$ wherein R_4 is as defined therein and R_5 is alkylene or R_3 is $R_6-S(O)_2-R_7-$ wherein R_7 is alkylene and R_6 is as defined therein.

5. The compound according to Claim 1 wherein

R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl,

R_1 is selected from the group consisting of

(i) alkoxyalkyl, (ii) cycloalkyl, (iii) phenyl, (iv) pyridyl, (v) furanyl or (vi) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl,

4-ethoxyphenyl, 4-propoxyphenyl,4-isopropxyphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl,1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofurnayl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is R_4-C(O)-R_5- wherein R_4 is as defined therein and R_5 is alkylene.

6. The compound according to Claim 1 wherein

R is -$C(O)_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-$NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl,

R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is R_4-C(O)-R_5- wherein R_4 is as defined therein and R_5 is alkylene.

7. The compound according to Claim 1 wherein

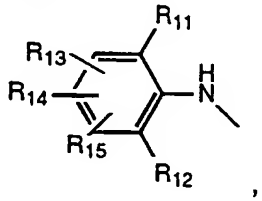
R is -$C(O)_2$-G wherein G is hydrogen or a carboxy protecting group,

R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-

propoxyphenyl, 4-isopropoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is R_4-C(O)-R_5- wherein R_4 is



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wherein R_{11} and R_{12} are independently selected from the group consisting of loweralkyl and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is alkylene.

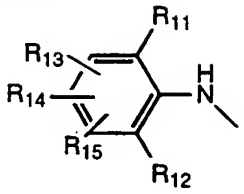
8. The compound according to Claim 1 wherein

R is -$C(O)_2$-G wherein G is hydrogen or a carboxy protecting group,

R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is R_4-C(O)-R_5- wherein R_4 is



wherein R_{11} and R_{12} are independently selected from the group consisting of loweralkyl, alkoxy and halo, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano, and R_5 is alkylene.

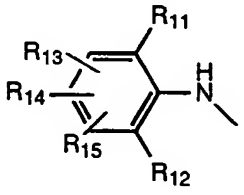
9. The compound according to Claim 1 wherein

R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group,

R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

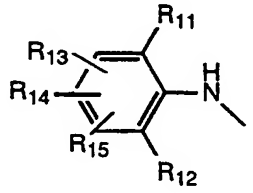
R_3 is R_4-C(O)-R_5- wherein R_4 is



wherein R_{11} and R_{12} are independently selected from the group consisting of methyl, ethyl, and isopropyl, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl,

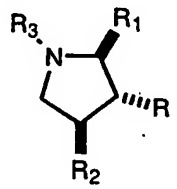
heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is alkylene.

10. The compound according to Claim 1 wherein
R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,
R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,
R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and
R_3 is $R_4-C(O)-R_5-$ wherein R_4 is



wherein R_{11} and R_{12} are independently selected from the group consisting of methyl, ethyl, and isopropyl, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is methylene.

11. The compound according to Claim 1 of the formula:



wherein

R is $-(CH_2)_m-W$ wherein m is an integer from 0 to 6 and W is

(a) $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

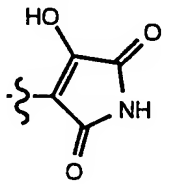
(i) hydroxy,

(j) alkoxy,

(k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,

(m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,

(n) 

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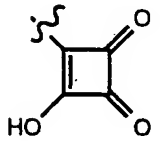
(o) 

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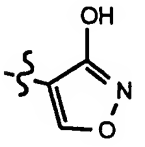
(p) 

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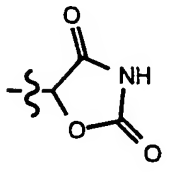
(q) 

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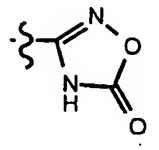
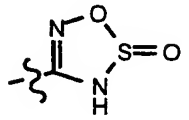
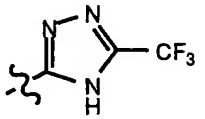
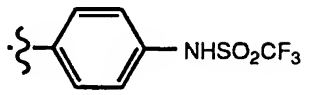
(r)  ,

(s)  ,

(t)  , or

(u)  ;

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N\text{-}R_{cc}$- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

R_3 is $R_4\text{-}C(O)\text{-}R_5$- or $R_6\text{-}S(O)_2\text{-}R_7$-

wherein R_5 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) $-N(R_{20})\text{-}R_8$- or -$R_{8a}\text{-}N(R_{20})\text{-}R_8$-

wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene and alkenylene and

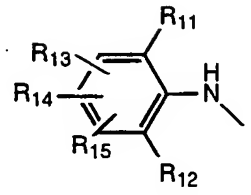
R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl or cycloalkylalkyl or (v) $-O\text{-}R_9$- or -$R_{9a}\text{-}O\text{-}R_9$- wherein R_9 and R_{9a} are independently selected from alkylene;

R_7 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{21})\text{-}R_{10}$- or -$R_{10a}\text{-}N(R_{21})\text{-}R_{10}$- wherein R_{10} and

R_{10a} are independently selected from the group consisting of alkylene and alkenylene and

R_{21} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

wherein R_4 and R_6 are



(i) ,

wherein R_{11} and R_{12} are independently selected from the group consisting of loweralkyl, cyano, halo, alkoxy, haloalkyl and phenyl and R_{13},R_{14},R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano; or

(ii) heterocyclic(amino),

or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 11 wherein

R_3 is R_4-C(O)-R_5- wherein R_4 is as defined therein and R_5 is alkylene or R_3 is R_6-$S(O)_2$-R_7- wherein R_7 is alkylene and R_6 is as defined therein.

13. The compound according to Claim 11 wherein

R is -$C(O)_2$-G wherein G is hydrogen or a carboxy protecting group or R is tetrazolyl or R is -C(O)-$NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl,

R_1 and R_2 are independently selected from

(i) loweralkyl, (ii) cycloalkyl, (iii) substituted or unsubstituted aryl and (iv) substituted or unsubstituted heterocyclic, and

R_3 is R_4-C(O)-R_5- wherein R_4 is as defined therein and R_5 is alkylene or R_3 is R_6-$S(O)_2$-R_7- wherein R_7 is alkylene and R_6 is as defined therein.

14. The compound according to Claim 11 wherein

R is -$C(O)_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-$NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl,

R_1 is (i) alkoxyalkyl, (ii) cycloalkyl, (iii) phenyl, (iv) pyridyl, (v) furanyl or (vi) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-

ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is R_4-C(O)-R_5- wherein R_4 is as defined therein and R_5 is alkylene or R_3 is R_6-$S(O)_2$-R_7- wherein R_7 is alkylene and R_6 is as defined therein.

15. The compound according to Claim 11 wherein

R is $-C(O)_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-$NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl,

R_1 is selected from the group consisting of

(i) alkoxyalkyl, (ii) cycloalkyl, (iii) phenyl, (iv) pyridyl, (v) furanyl or (vi) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-propoxyphenyl,4-isopropxypheyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 2-fluoro-4ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is substituted or unsubstituted 1,3-benzodioxolyl,

7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofurnayl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is R_4-C(O)-R_5- wherein R_4 is as defined therein and R_5 is alkylene.

16. The compound according to Claim 11 wherein

R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl,

R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is $R_4-C(O)-R_5-$ wherein R_4 is as defined therein and R_5 is alkylene.

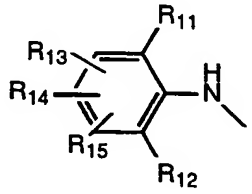
17. The compound according to Claim 11 wherein

R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,

R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

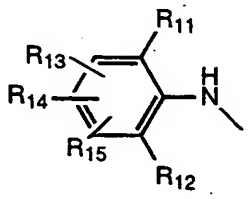
R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is $R_4-C(O)-R_5-$ wherein R_4 is



wherein R_{11} and R_{12} are independently selected from the group consisting of loweralkyl and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is alkylene.

18. The compound according to Claim 11 wherein
R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,
R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxphenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,
R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and
R_3 is $R_4-C(O)-R_5-$ wherein R_4 is



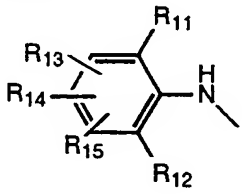
wherein R_{11} and R_{12} are independently selected from the group consisting of loweralkyl, alkoxy and halo, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano, and R_5 is alkylene.

19. The compound according to Claim 11 wherein
R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,

R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2 methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2 isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is R_4-C(O)-R_5- wherein R_4 is



wherein R_{11} and R_{12} are independently selected from the group consisting of methyl, ethyl, and isopropyl, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, alkylsulfonyl, arylsulfonyl, thioalkoxy, thioaryloxy, or cyano and R_5 is alkylene.

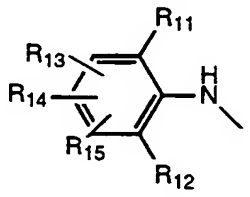
20. The compound according to Claim 11 wherein

R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group,

R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-isopropoxyphenyl, 2-fluoro-4-ethoxyphenyl, 3-fluoro-4-propoxyphenyl, 3-methoxy-4-propoxyphenyl, 4-methoxymethoxyphenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-ethoxyethoxy)phenyl, 4-(2-isopropoxyethoxy)phenyl, 4-hydroxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,

R_2 is 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and

R_3 is R_4-C(O)-R_5- wherein R_4 is



wherein R_{11} and R_{12} are independently selected from the group consisting of methyl, ethyl, and isopropyl, and R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, loweralkyl, hydroxy, amino, alkoxy, aryl, heterocyclic, halo, carboxy, nitro, or cyano and R_5 is methylene.

21. A compound selected from the group consisting of

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-methoxy-4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-propoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

trans,trans-2-(3-methoxy-4-propoxyphenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

[*2R,3R,4S*]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
and (2*R*,3*R*,4*S*)-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-isopropoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(2-fluoro-4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
trans,trans-2-(4-(2-Ethoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2R,3R,4S]-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
[2R,3R,4S]-2-(4-(2-Ethoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, and
trans,trans-2-(4-(2-isopropoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid,
or a pharmaceutically acceptable salt thereof.

22. A compound of claim 21 wherein said compound is *trans,trans*-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
or a pharmaceutically acceptable salt thereof.

23. A compound of claim 21 wherein said compound is [*2R,3R,4S*]2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

24. A compound of claim 21 wherein said compound is [*2R,3R,4S*]2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((2,6-

diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

25. A compound of claim 21 wherein said compound is (2*R*,3*R*,4*S*)-2-(4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((2,6-diethyl)phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

26. A compound of claim 21 wherein said compound is *trans,trans*-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(2, 6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof

27. A pharmaceutical composition for antagonizing endothelin comprising a therapeutically effective amount of the compound of Claim 1 and a pharmaceutically acceptable carrier.

28. A pharmaceutical composition for antagonizing endothelin comprising a therapeutically effective amount of the compound of Claim 11 and a pharmaceutically acceptable carrier.

29. A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

30. A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 11.

31. A method for treating treating hypertension, congestive heart failure, restenosis following arterial injury, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

32. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 11.

33. A method for treating treating coronary angina, cerebral vasospasm, acute and chronic pulmonary hypertension, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, fibrotic or proliferative diseases, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-repurfusion injury, systemic sclerosis, liver cirrhosis, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, schleroderma, prostatic hyperplasia, cardiac hyperplasia, Raynaud's disease, cancers, adenocarcinomas, angina, transplant-induced artherosclerosis, and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

34. A method for treating treating coronary angina, cerebral vasospasm, acute and chronic pulmonary hypertension, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, fibrotic or proliferative diseases, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-repurfusion injury, systemic sclerosis, liver cirrhosis, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, schleroderma, prostatic hyperplasia, cardiac hyperplasia, Raynaud's disease, cancers, adenocarcinomas, angina, transplant-induced arterosclerosis, and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 11.

35. A method for treating treating hypertension, congestive heart failure, restenosis following arterial injury, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a

therapeutically effective amount of a compound of Claim 1 in combination with one or more cardiovascular agents.

36. A method for treating treating hypertension, congestive heart failure, restenosis following arterial injury, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 11 in combination with one or more cardiovascular agents.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/11821

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/16 C07D405/04 A61K31/40

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06095 A (ABBOTT LABORATORIES) 29 February 1996 see examples 10,13,45,121,132,173, 208,209,221,226,238,276,279,291,298, 316, Tables 2,2A, claims	1-36
P,X	WO 97 30046 A (ABBOTT LABORATORIES) 21 August 1997 see claims; examples	1-36

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1998	09. 10. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helps, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte.. ational application No.
PCT/US 98/11821

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28-36 are drawn to methods of treatment of the human or animal body by therapy, the search has been carried out based on the alleged effects of the compounds and compositions.

2. [X] Claims Nos.: 1-5(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the very broad scope of the claims, the search was limited to the scope covered by the prepared examples (see Guidelines, B-III, 3.7).

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Im. ational Application No
PCT/US 98/11821

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606095 A	29-02-1996	US 5767144 A	16-06-1998
		AU 3213795 A	14-03-1996
		CA 2195677 A	29-02-1996
		EP 0776324 A	04-06-1997
		JP 10504565 T	06-05-1998
		US 5622971 A	22-04-1997
		US 5731434 A	24-03-1998
WO 9730046 A	21-08-1997	AU 2267897 A	02-09-1997